(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 269 994 A2

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
02.01.2003 Bulletin 2003/01

(51) Int Cl.⁷: A61K 9/14

(21) Application number: 02253951.4

(22) Date of filing: 06.06.2002

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: 22.06.2001 US 300314 P

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(54) Pharmaceutical compositions comprising drug and concentration-enhancing polymers

(57) A solubility-improved drug form is combined with a concentration-enhancing polymer in a sufficient amount so that the combination provides substantially enhanced drug concentration in a use environment relative to a control comprising the same amount of the same drug form without the concentration-enhancing polymer.

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[0014] Usui, et al., *Inhibitory Effects of Water-soluble Polymers on Precipitation of RS-8359*, Int'l J. of Pharmaceutics 154 (1997) 59-66, discloses the use of three polymers, namely hydroxy propyl methyl cellulose, hydroxy propyl cellulose, and polyvinylpyrrolidone to inhibit precipitation of the low-solubility drug RS-8359. The drug and polymer were dissolved in a mixture of 0.5 N HCl and methanol, and then added to a phosphate buffer solution. Usui et al. observed that the particular polymers inhibited crystallization of the drug.

[0015] Nevertheless, what is still needed is a composition comprising a low-solubility drug that provides enhanced concentration of the drug in aqueous solution and/or that enhances the bioavailability of the drug. These needs and others that will become apparent to one of ordinary skill in the art are met by the present invention, which is summarized and described in detail below.

SUMMARY OF THE INVENTION

[0016] The invention relates to compositions comprising a combination of a drug in a solubility-improved form and at least one concentration-enhancing polymer that enhances the concentration of the drug in a use environment relative to control compositions that are free from the concentration-enhancing polymer. The terms "solubility-improved" and "solubility-improved drug form" as employed herein refer to a form of the drug that has increased solubility or dissolution rate relative to the least soluble form of the drug known. Thus, the term implies that a less soluble or more slowing dissolving form of the drug exists and is either known or has been determined, *i.e.*, known, for example, from the scientific or patent literature, or determined by or otherwise known to the investigator. The drug in the solubility-improved form provides a dissolved drug concentration in a use environment that exceeds, at least temporarily, the equilibrium concentration of the drug in the use environment. By "equilibrium concentration" is meant the dissolved drug concentration provided by the lowest solubility form of the drug alone, either crystalline or amorphous, in the use environment. In other words, the solubility-improved form is capable of achieving, at least temporarily, a supersaturated concentration of said drug in said use environment. Where the lowest solubility form of the drug provides a drug concentration that decreases slowly with respect to time in the use environment, it may be difficult to establish the lowest dissolved drug value that would represent the equilibrium concentration of the drug. In such cases, the equilibrium concentration of drug may be taken as the dissolved drug concentration in the use environment 20 hours after introduction of the drug to the use environment. A solubility-improved drug form also includes formulations that increase the rate of dissolution of the drug, leading to an initially higher concentration of drug in solution, at least temporarily, compared with the drug in its lowest solubility form.

[0017] A solubility-improved drug form may consist of a highly soluble form of the drug alone, may be a composition comprising a highly soluble form of the drug plus inert excipients, or may be a composition comprising the drug in a poorly or highly soluble form and one or more excipients which have the effect of increasing the solubility of the drug, regardless of the length of time for which the solubility is increased. Examples of "solubility-improved drug forms" include but are not limited to: (1) drug in microparticulate form; (2) drug in nanoparticulate form; (3) absorbed drug; (4) drug in a nanosuspension; (5) a supercooled melt of drug; (6) cyclodextrin/drug form; (7) softgel form; (8) gelatin form, (9) self-emulsifying form; and (10) three-phase drug form. (The drug in the solubility-improved form is.....sometimes referred to herein as simply "drug form.")

[0018] An object of the invention is to provide a pharmaceutically acceptable composition comprising (a) a drug in a solubility-improved form; and (b) a concentration-enhancing polymer combined with the drug in a sufficient amount so that the composition provides, after introduction to a use environment, a dissolution area under the concentration versus time curve ("AUC"), for any period of at least 90 minutes between the time of introduction into the use environment and about 270 minutes following introduction to the use environment that is at least 1.25-fold the corresponding AUC provided by a control composition, wherein the control composition is an equivalent quantity of the drug in the same solubility-improved form alone, but free from a concentration enhancing polymer.

[0019] Yet another object of the invention is to provide a pharmaceutically acceptable composition comprising (a) a drug in a solubility-improved form; and (b) a concentration-enhancing polymer combined with the drug in a sufficient amount so that the composition provides, after introduction to a use environment, a relative bioavailability of at least 1.25 relative to a control composition of an equivalent quantity of the drug in the same solubility-improved form alone but free from a concentration-enhancing polymer.

[0020] A method is also provided of administering a drug comprising co-administering: (a) a drug in a solubility-improved form; and (b) a concentration-enhancing polymer; wherein the concentration-enhancing polymer is co-administered with the drug in a sufficient amount so that, after introduction to a use environment, a dissolution area under the concentration versus time curve in the use environment for any period of at least 90 minutes between the time of introduction into the use environment and about 270 minutes following introduction to the use environment that is at least 1.25-fold the corresponding area under the curve provided by a control composition; and wherein the control composition is an equivalent quantity of the drug in the same solubility-improved form alone, but free from the concentration-enhancing polymer.

polymer, which is in a separate dosage form. The time difference between administration of the drug form and the concentration-enhancing polymer is such that they come into physical contact in the use environment. When they are not co-administered at the same time it is generally preferable to administer the concentration-enhancing polymer prior to administration of the drug form.

[0030] The various aspects and embodiments of the invention may be described as follows.

[0031] In a first aspect, the invention relates to a composition comprising:

(a) a drug in a solubility-improved form which provides, when administered to a use environment, at least one of a dissolved drug concentration in said use environment that exceeds an equilibrium concentration of a lowest solubility form of said drug in said use environment and a dissolution rate that exceeds a dissolution rate of said lowest solubility form of said drug in said use environment; and

(b) a concentration-enhancing polymer wherein said concentration-enhancing polymer is present in a sufficient amount so that said composition provides, after introduction to said use environment, a maximum concentration of said drug in said use environment that is at least 1.25-fold a maximum concentration of said drug provided by a control composition, wherein said control composition is an equivalent quantity of said drug in said solubility-improved form alone.

[0032] In a second aspect, the invention relates to a composition comprising:

(a) a drug in a solubility-improved form which provides, when administered to a use environment, at least one of a dissolved drug concentration in said use environment that exceeds an equilibrium concentration of a lowest solubility form of said drug in said use environment and a dissolution rate that exceeds a dissolution rate of said lowest solubility form of said drug in said use environment; and

(b) a concentration-enhancing polymer;

wherein said concentration-enhancing polymer is present in a sufficient amount so that said composition provides, after introduction to a use environment, a dissolution area under the concentration versus time curve for any period of at least 90 minutes between the time of introduction into the use environment and about 270 minutes following introduction to the use environment that is at least 1.25-fold the corresponding area under the curve provided by a control composition, wherein said control composition is an equivalent quantity of said drug in said solubility-improved form alone.

[0033] In a third aspect, the invention relates to a composition comprising:

(a) a drug in a solubility-improved form which provides, when administered to a use environment, at least one of a dissolved drug concentration in said use environment that exceeds an equilibrium concentration of a lowest solubility form of said drug in said use environment and a dissolution rate that exceeds a dissolution rate of said lowest solubility form of said drug in said use environment; and

(b) a concentration-enhancing polymer;

wherein said concentration-enhancing polymer is present in a sufficient amount so that said composition provides, after introduction to said use environment, a relative bioavailability of at least 1.25 relative to a control composition, wherein said control composition is an equivalent quantity of said drug in said solubility-improved form alone.

[0034] In further independent embodiments of the first, second and third aspects of the invention, the solubility-improved drug form is selected from the group consisting of drug in microparticulate form, drug in nanoparticulate form, absorbed drug, drug in a nanosuspension, a supercooled melt of drug, cyclodextrin/drug form, softgel form, gelatin form, self-emulsifying form, and three-phase drug form.

[0035] In further independent embodiments of the first , second and third aspects of the invention, the drug is in nanoparticulate form. The nanoparticulate form of the drug may comprise particles of 10% to 99.9% by weight of a crystalline drug substance having a solubility in water of less than 10 mg/ml, said drug substance having an effective average particle size of less than about 400 nm. In one embodiment, nanoparticulate form of the drug consists essentially of 10% to 99.9% by weight of a crystalline drug substance having a solubility in water of less than 10 mg/mL, said drug substance having a non-crosslinked surface modifier adsorbed on the surface thereof in an amount of 0.1 to 90% by weight and sufficient to maintain an effective average particle size of less than about 400 nm.

[0036] In further independent embodiments of the first, second and third aspects of the invention,the drug is selected from the group consisting of antihypertensives, antianxiety agents, anticlotting agents, anticonvulsants, blood glucose-lowering agents, decongestants, antihistamines, antitussives, antineoplastics, beta blockers, anti-inflammatories, antipsychotic agents, cognitive enhancers, cholesterol-reducing agents, antiobesity agents, autoimmune disorder agents, anti-impotence agents, antibacterial and antifungal agents, hypnotic agents, anti-Parkinsonism agents, anti-Alzheim-

(a) a drug in a solubility-improved form which provides, when administered to a use environment, at least one of a dissolved drug concentration in said use environment that exceeds an equilibrium concentration of a lowest solubility form of said drug in said use environment and a dissolution rate that exceeds a dissolution rate of said lowest solubility form of said drug in said use environment; and
(b) a concentration-enhancing polymer;

wherein said concentration-enhancing polymer is co-administered with said drug in a sufficient amount, so that after introduction to said use environment, a maximum concentration of said drug in said use environment is provided that is at least 1.25-fold a maximum concentration of said drug provided by a control composition, wherein said control composition is an equivalent quantity of said drug in said solubility-improved form alone.

[0049] In a fifth aspect, the invention relates to a method of administering a low-solubility drug comprising co-administering:

(a) a drug in a solubility-improved form which provides, when administered to a use environment, at least one of a dissolved drug concentration in said use environment that exceeds an equilibrium concentration of a lowest solubility form of said drug in said use environment and a dissolution rate that exceeds a dissolution rate of said lowest solubility form of said drug in said use environment; and
(b) a concentration-enhancing polymer;

wherein said concentration-enhancing polymer is co-administered with said drug in a sufficient amount so that, after introduction to said environment, a dissolution area under the concentration versus time curve for any period of at least 90 minutes between the time of introduction into the use environment and about 270 minutes following introduction to the use environment is provided that is at least 1.25-fold the corresponding area under the curve provided by a control composition;

and wherein said control composition is an equivalent quantity of said drug in said solubility-improved form alone.

[0050] In a sixth aspect, the invention relates to a method of administering a low-solubility drug comprising co-administering:

(a) a drug in a solubility-improved form which provides, when administered to a use environment, at least one of a dissolved drug concentration in said use environment that exceeds an equilibrium concentration of a lowest solubility form of said drug in said use environment and a dissolution rate that exceeds a dissolution rate of said lowest solubility form of said drug in said use environment; and
(b) a concentration-enhancing polymer;

wherein said concentration-enhancing polymer is co-administered with said drug in a sufficient amount so that, after introduction to said use environment, a relative bioavailability is provided that is at least 1.25-fold that of a control composition, wherein said control composition is an equivalent quantity of said drug in said solubility-improved form alone.

[0051] In further independent embodiments of the fourth, fifth and sixth aspects of the invention, the solubility-improved drug form is selected from the group consisting of in nanoparticulate form, absorbed drug, drug in a nanosuspension, a supercooled melt of drug, cyclodextrin/drug form, softgel form, self-emulsifying form, and three-phase drug form.

[0052] In further independent embodiment of the fourth, fifth, and sixth aspects of the invention, the drug is in nanoparticulate form. The nanoparticulate form of the drug may comprise particles of 10% to 99.9% by weight of a crystalline drug substance having a solubility in water of less than 10 mg/ml, said drug substance having an effective average particle size of less than about 400 nm. In one embodiment, nanoparticulate form of the drug consists essentially of 10% to 99.9% by weight of a crystalline drug substance having a solubility in water of less than 10 mg/mL, said drug substance having a non-crosslinked surface modified adsorbed on the surface thereof in an amount of 0.1 to 90% by weight and sufficient to maintain an effective particle size of less than about 400 nm.

[0053] In further independent embodiments of the fourth, fifth and sixth aspects of the invention, the drug may be selected from the group consisting of antihypertensives, antianxiety agents, anticlotting agents, anticonvulsants, blood glucose-lowering agents, decongestants, antihistamines, antitussives, antineoplastics, beta blockers, anti-inflammatories, antipsychotic agents, cognitive enhancers, cholesterol-reducing agents, antiobesity agents, autoimmune disorder agents, anti-impotence agents, antibacterial and antifungal agents, hypnotic agents, anti-Parkinsonism agents, anti-Alzheimer's disease agents, antibiotics, anti-depressants, antiviral agents, anti-atherosclerotic agents, glycogen phosphorylase inhibitors, and cholesterol ester transfer protein inhibitors.

[0054] In further independent embodiments of the fourth, fifth and sixth aspects of the invention, the drug is a glycogen phosphorylase inhibitor selected from the group consisting of [R-(R*S*)]-5-chloro-N-[2-hydroxy-3-{methoxymethylami-

DETAILED DESCRIPTION OF THE INVENTION

[0066] The pharmaceutical compositions of the present invention comprise a combination of a solubility-improved form of drug and at least one concentration-enhancing polymer that enhances the concentration of the drug in a use environment relative to control compositions that are free from the concentration-enhancing polymer. Examples of solubility-improved drug forms are: (1) drug in microparticulate form; (2) drug in nanoparticulate form; (3) absorbed drug; (4) drug in a nanosuspension; (5) a supercooled melt of drug; (6) cyclodextrin/drug form; (7) softgel form; (8) gelatin form, (9) self-emulsifying form; and (10) three-phase drug form. Suitable drugs, methods to form the solubility-improved drug forms, concentration-enhancing polymers, as well as methods for preparing the compositions, and methods for coadministration are discussed in detail below.

THE DRUG

[0067] The present invention is useful with any drug capable of being formulated in one of the above solubility-improved drug forms. The term "drug" is conventional, denoting a compound having beneficial prophylactic and/or therapeutic properties when administered to an animal, especially humans. The drug does not need to be sparingly soluble in order to benefit from this invention, although sparingly soluble drugs represent a preferred class for use with the invention. Even a drug that nonetheless exhibits appreciable solubility in the desired environment of use can benefit from the increased solubility/bioavailability made possible by this invention if the addition of the concentration-enhancing polymer can reduce the size of the dose needed for therapeutic efficacy or increase the rate of drug absorption in cases where a rapid onset of the drug's effectiveness is desired.

[0068] The present invention finds particular utility when the drug is a "low-solubility drug," meaning that the drug may be either "substantially water-insoluble," which means that the drug has a minimum aqueous solubility at physiologically relevant pH (*e.g.,* pH 1-8) of less than 0.01 mg/mL, "sparingly water-soluble," that is, has an aqueous solubility up to about 1 to 2 mg/mL, or even low to moderate aqueous-solubility, having an aqueous-solubility from about 1 mg/mL to as high as about 20 to 40 mg/mL. The invention finds greater utility as the solubility of the drug decreases. Thus, compositions of the present invention are preferred for low-solubility drugs having a solubility of less than 10 mg/mL, more preferred for low-solubility drugs having a solubility of less than 1 mg/mL, and even more preferred for low-solubility drugs having a solubility of less than 0.1 mg/mL. In general, it may be said that the drug has a dose-to-aqueous solubility ratio greater than 10 mL, and more typically greater than 100 mL, where the drug solubility (mg/mL) is the minimum value observed in any physiologically relevant aqueous solution (*e.g.,* those with pH values between 1 and 8) including USP simulated gastric and intestinal buffers, and the dose is in mg. Thus, a dose-to-aqueous-solubility ratio may be calculated by dividing the dose (in mg) by the solubility (in mg/mL).

[0069] Preferred classes of drugs include, but are not limited to, antihypertensives, antianxiety agents, anticlotting agents, anticonvulsants, blood glucose-lowering agents, decongestants, antihistamines, antitussives, antineoplastics, beta blockers, anti-inflammatories, antipsychotic agents, cognitive enhancers, cholesterol-reducing agents, anti-atherosclerotic agents, antiobesity agents, autoimmune disorder agents, anti-impotence agents, antibacterial and antifungal agents, hypnotic agents, anti-Parkinsonism agents, anti-Alzheimer's disease agents, antibiotics, anti-depressants, antiviral agents, glycogen phosphorylase inhibitors, and cholesterol ester transfer protein inhibitors.

[0070] Each named drug should be understood to include the neutral form of the drug, pharmaceutically acceptable salts, as well as prodrugs. Specific examples of antihypertensives include prazosin, nifedipine, amlodipine besylate, trimazosin and doxazosin; specific examples of a blood glucose-lowering agent are glipizide and chlorpropamide; a specific example of an anti-impotence agent is sildenafil and sildenafil citrate; specific examples of antineoplastics include chlorambucil, lomustine and echinomycin; a specific example of an imidazole-type antineoplastic is tubulazole; a specific example of an anti-hypercholesterolemic is atorvastatin and atorvastatin calcium; specific examples of anxiolytics include hydroxyzine hydrochloride and doxepin hydrochloride; specific examples of anti-inflammatory agents include betamethasone, prednisolone, aspirin, piroxicam, valdecoxib, carprofen, celecoxib, flurbiprofen and (+)-N-{4-[3-(4-fluorophenoxy)phenoxy]-2-cyclopenten-1-yl}-N-hyroxyurea; a specific example of a barbiturate is phenobarbital; specific examples of antivirals include acyclovir, nelfinavir, and virazole; specific examples of vitamins/nutritional agents include retinol and vitamin E; specific examples of beta blockers include timolol and nadolol; a specific example of an emetic is apomorphine; specific examples of a diuretic include chlorthalidone and spironolactone; a specific example of an anticoagulant is dicumarol; specific examples of cardiotonics include digoxin and digitoxin; specific examples of androgens include 17-methyltestosterone and testosterone; a specific example of a mineral corticoid is desoxycorticosterone; a specific example of a steroidal hypnotic/anesthetic is alfaxalone; specific examples of anabolic agents include fluoxymesterone and methanstenolone; specific examples of antidepression agents include sulpiride, [3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-(1-ethylpropyl)-amine, 3,5-dimethyl-4-(3'-pentoxy)-2-(2',4',6'-trimethylphenoxy)pyridine, pyroxidine, fluoxetine, paroxetine, venlafaxine and sertraline; specific examples of antibiotics include carbenicillin indanylsodium, bacampicillin hydrochloride, troleandomycin, doxycyline hyclate, ampicillin

drug levels in the blood by oral dosing of practical quantities of drug generally requires a large enhancement in drug concentrations in the gastrointestinal fluid and a resulting large enhancement in bioavailability. Such enhancements in drug concentration in gastrointestsinal fluid typically need to be at least about 10-fold and often at least about 50-fold or even at least about 200-fold to achieve desired blood levels. Surprisingly, the formulations of the present invention have proven to have the required large enhancements in drug concentration and bioavailability.

[0075] In contrast to conventional wisdom, the relative degree of enhancement in aqueous concentration and bioavailability generally improves for CETP inhibitors as solubility decreases and hydrophobocity increases. In fact, the inventors have recognized a subclass of these CETP inhibitors that are essentially aqueous insoluble, highly hydrophobic, and are characterized by a set of physical properties. This subclass exhibits dramatic enhancements in aqueous concentration and bioavailability when formulated using the compositions of the present invention.

[0076] The first property of this subclass of essentially insoluble, hydrophobic CETP inhibitors is extremely low aqueous solubility. By extremely low aqueous solubility is meant that the minimum aqueous solubility at physiologically relevant pH (pH of 1 to 8) is less than about 10 μg/ml and preferably less than about 1 μg/ml.

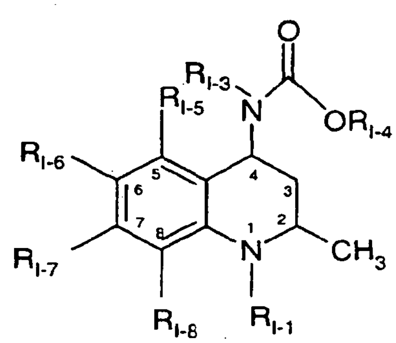
[0077] A second property is a very high does-to-solubility ratio. Extremely low solubility often leads to poor or slow absorption of the drug from the fluid of the gastrointestinal tract, when the drug is dosed orally in a conventional manner. For extremely low solubility drugs, poor absorption generally becomes progressively more difficult as the dose (mass of drug given orally) increases. Thus, a second property of this subclass of essentially insoluble, hydrophobic CETP inhibitors is a very high dose (in mg) to solubility (in mg/ml) ratio (ml). By "very high dose-to-solubility ratio" is meant that the dose-to-solubility ratio has a value of at least 1000 ml, and preferably at least 5,000 ml, and more preferably at least 10,000 ml.

[0078] A third property of this subclass of essentially insoluble, hydrophobic CETP inhibitors is that they are extremely hydrophobic. By extremely hydrophobic is meant that the Clog P value of the drug, has a value of at least 4.0, preferably a value of at least 5.0, and more preferably a value of at least 5.5.

[0079] A fourth property of this subclass of essentially insoluble CETP inhibitors is that they have a low melting point. Generally, drugs of this subclass will have a melting point of about 150°C or less, and preferably about 140°C or less.

[0080] Primarily, as a consequence of some or all of these four properties, CETP inhibitors of this subclass typically have very low absolute bioavailabilities. Specifically, the absolute bioavailibility of drugs in this subclass when dosed orally in their undispersed state is less than about 10% and more often less than about 5%.

[0081] Turning now to the chemical structures of specific CETP inhibitors, one class of CETP inhibitors that finds utility with the present invention consists of oxy substituted 4-carboxyamino-2-methyl-1,2,3,4-tetrahydroquinolines having the Formula I



Formula I

and pharmaceutically acceptable salts, enantiomers, or stereoisomers of said compounds;

wherein R_{I-1} is hydrogen, Y_I, W_I-X_I, W_I-Y_I;

wherein W_I is a carbonyl, thiocarbonyl, sulfinyl or sulfonyl;

X_I is -O-Y_I, -S-Y_I, -N(H)-Y_I or -N-$(Y_I)_2$;

wherein Y_I for each occurrence is independently Z_I or a fully saturated, partially unsaturated or fully unsaturated one to ten membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may

alkenyl, hydroxy, (C_1-C_6)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6)alkylamino wherein said (C_1-C_6)alkyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy, (C_1-C_6)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6)alkylamino, said (C_1-C_6)alkyl substituent is also optionally substituted with from one to nine fluorines.

[0082] Compounds of Formula I and their methods of manufacture are disclosed in commonly assigned United States Patent No. 6,140,342, United States Patent No. 6,362,198, and European Patent publication 987251, all of which are incorporated herein by reference in their entireties for all purposes.

[0083] In a preferred embodiment, the CETP inhibitor is selected from one of the following compounds of Formula I:

[2R,4S] 4-[(3,5-dichloro-benzyl)-methoxycarbonyl-amino]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
[2R,4S] 4-[(3,5-dinitro-benzyl)-methoxycarbonyl-amino]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
[2R,4S] 4-[(2,6-dichloro-pyridin-4-ylmethyl)-methoxycarbonyl-amino]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
[2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
[2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6-methoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
[2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-7-methoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester,
[2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
[2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-ethoxycarbonyl-amino]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
[2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2,2,2-trifluoro-ethylester;
[2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid propyl ester;
[2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester;
[2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-methyl-6-trifluoromethoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester,
[2R,4S] (3,5-bis-trifluoromethyl-benzyl)-(1-butyryl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid methyl ester;
[2R,4S] (3,5-bis-trifluoromethyl-benzyl)-(1-butyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid methyl ester; and
[2R,4S] (3,5-bis-trifluoromethyl-benzyl)-[1-(2-ethyl-butyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-carbamic acid methyl ester, hydrochloride.

[0084] Another class of CETP inhibitors that finds utility with the present invention consists of 4-carboxyamino-2-methyl-1,2,3,4,-tetrahydroquinolines, having the Formula II

selected from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo, and said carbon chain is optionally mono-substituted with V_{II-1};

wherein V_{II-1} is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said V_{II-1} substituent is optionally mono-, di-, tri-, or tetra-substituted independently with halo, (C_1-C_6) alkyl, (C_1-C_6)alkoxy, amino, nitro, cyano, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6)alkylamino wherein said (C_1-C_6)alkyl substituent is optionally mono-substituted with oxo, said (C_1-C_6)alkyl substituent is optionally substituted with from one to nine fluorines;

wherein either R_{II-3} must contain V_{II} or R_{II-4} must contain V_{II-1}; and

R_{II-5}, R_{II-6}, R_{II-7} and R_{II-8} are each independently hydrogen, a bond, nitro or halo wherein said bond is substituted with T_{II} or a partially saturated, fully saturated or fully unsaturated (C_1-C_{12}) straight or branched carbon chain wherein carbon may optionally be replaced with one or two heteroatoms selected independently from oxygen, sulfur and nitrogen wherein said carbon atoms are optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo, and said carbon is optionally mono-substituted with T_{II};

wherein T_{II} is a partially saturated, fully saturated or fully unsaturated three to twelve membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or, a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

wherein said T_{II} substituent is optionally mono-, di- or tri-substituted independently with halo, (C_1-C_6)alkyl, (C_2-C_6) alkenyl, hydroxy, (C_1-C_6)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6)alkylamino wherein said (C_1-C_6)alkyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy, (C_1-C_6)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6)alkylamino, said (C_1-C_6)alkyl substituent is also optionally substituted with from one to nine fluorines;

provided that at least one of substituents R_{II-5}, R_{II-6}, R_{II-7} and R_{II-8} is not hydrogen and is not linked to the quinoline moiety through oxy.

[0085] Compounds of Formula II and their methods of manufacture are disclosed in commonly assigned United States Patent No. 6,147,090, United States Patent Application No. 09/671,400 filed September 27, 2000, and PCT Publication No. WO00/17166, all of which are incorporated herein by reference in their entireties for all purposes.

[0086] In a preferred embodiment, the CETP inhibitor is selected from one of the following compounds of Formula II:

[2R,4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-methyl-7-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

[2R,4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-7-chloro-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

[2R,4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6-chloro-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

[2R,4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2,6,7-trimethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

[2R,4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6,7-diethyl-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

[2R,4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6-ethyl-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

[2R,4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester; and

[2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.

[0087] Another class of CETP inhibitors that finds utility with the present invention consists of annulated 4-carboxyamino-2-methyl-1,2,3,4,-tetrahydroquinolines, having the Formula III

sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo, and said carbon chain is optionally mono-substituted with V_{III-1};

wherein V_{III-1} is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said V_{III-1} substituent is optionally mono-, di-, tri-, or tetra-substituted independently with halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, amino, nitro, cyano, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6)alkylamino wherein said (C_1-C_6)alkyl substituent is optionally mono-substituted with oxo, said (C_1-C_6)alkyl substituent optionally having from one to nine fluorines;

wherein either R_{III-3} must contain V_{III} or R_{III-4} must contain V_{III-1}; and

R_{III-5} and R_{III-6}, or R_{III-6} and R_{III-7}, and/or R_{III-7} and R_{III-8} are taken together and form at least one four to eight membered ring that is partially saturated or fully unsaturated optionally having one to three heteroatoms independently selected from nitrogen, sulfur and oxygen;

wherein said ring or rings formed by R_{III-5} and R_{III-6}, or R_{III-6} and R_{III-7}, and/or R_{III-7} and R_{III-8} are optionally mono-, di- or tri-substituted independently with halo, (C_1-C_6)alkyl, (C_1-C_4)alkylsulfonyl, (C_2-C_6)alkenyl, hydroxy, (C_1-C_6)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6)alkylamino wherein said (C_1-C_6)alkyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy, (C_1-C_6)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6)alkylamino, said (C_1-C_6)alkyl substituent optionally having from one to nine fluorines;

provided that the R_{III-5}, R_{III-6}, R_{III-7} and/or R_{III-8}, as the case may be, that do not form at least one ring are each independently hydrogen, halo, (C_1-C_6)alkoxy or (C_1-C_6)alkyl, said (C_1-C_6)alkyl optionally having from one to nine fluorines.

[0088] Compounds of Formula III and their methods of manufacture are disclosed in commonly assigned United States Patent No. 6,147,089, United States Patent No. 6,310,075, and European Patent Application No. 99307240.4 filed September 14, 1999, all of which are incorporated herein by reference in their entireties for all purposes.

[0089] In a preferred embodiment, the CETP inhibitor is selected from one of the following compounds of Formula III:

[2R, 4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-methyl-2,3,4,6,7,8-hexahydro-cyclopenta[g]quinoline-1-carboxylic acid ethyl ester;
[6R, 8S] 8-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6-methyl-3,6,7,8-tetrahydro-1H-2-thia-5-aza-cyclopenta[b]naphthalene-5-carboxylic acid ethyl ester;
[6R, 8S] 8-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6-methyl-3,6,7,8-tetrahydro-2H-furo[2,3-g]quinoline-5-carboxylic acid ethyl ester;
[2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-methyl-3,4,6,8-tetrahydro-2H-furo[3,4-g]quinoline-1-carboxylic acid ethyl ester;
[2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-methyl-3,4,6,7,8,9-hexahydro-2H-benzo[g]quinoline-1-carboxylic acid propyl ester;
[7R,9S] 9-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-7-methyl-1,2,3,7,8,9-hexahydro-6-aza-cyclopenta[a]naphthalene-6-carboxylic acid ethyl ester; and
[6S,8R] 6-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-8-methyl-1,2,3,6,7,8-hexahydro-9-aza-cyclopenta[a]naphthalene-9-carboxylic acid ethyl ester.

[0090] Another class of CETP inhibitors that finds utility with the present invention consists of 4-carboxyamino-2-substituted-1,2,3,4,-tetrahydroquinolines, having the Formula IV

selected from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo, and said carbon chain is optionally mono-substituted with V_{IV};

wherein V_{IV} is a partially saturated, fully saturated or fully unsaturated three to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

wherein said V_{IV} substituent is optionally mono-, di-, tri-, or tetra-substituted independently with halo, (C_1-C_6) alkyl, (C_2-C_6)alkenyl, hydroxy, (C_1-C_6)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxamoyl, mono-N- or di-N, N-(C_1-C_6) alkylcarboxamoyl, carboxy, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6)alkylamino wherein said (C_1-C_6)alkyl or (C_2-C_6)alkenyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy, (C_1-C_6) alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6) alkylamino, said (C_1-C_6)alkyl or (C_2-C_6)alkenyl substituents are also optionally substituted with from one to nine fluorines;

R_{IV-4} is Q_{IV-1} or V_{IV-1};

wherein Q_{IV-1} a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one heteroatom selected from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo, and said carbon chain is optionally mono-substituted with V_{IV-1};

wherein V_{IV-1} is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said V_{IV-1} substituent is optionally mono-, di-, tri-, or tetra-substituted independently with halo, (C_1-C_6) alkyl, (C_1-C_6)alkoxy, amino, nitro, cyano, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6)alkylamino wherein said (C_1-C_6)alkyl substituent is optionally mono-substituted with oxo, said (C_1-C_6)alkyl substituent is also optionally substituted with from one to nine fluorines;

wherein either R_{IV-3} must contain V_{IV} or R_{IV-4} must contain V_{IV-1}; R_{IV-5}, R_{IV-6}, R_{IV-7} and R_{IV-8} are each independently hydrogen, a bond, nitro or halo wherein said bond is substituted with T_{IV} or a partially saturated, fully saturated or fully unsaturated (C_1-C_{12}) straight or branched carbon chain wherein carbon, may optionally be replaced with one or two heteroatoms selected independently from oxygen, sulfur and nitrogen wherein said carbon atoms are optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo, and said carbon is optionally mono-substituted with T_{IV};

wherein T_{IV} is a partially saturated, fully saturated or fully unsaturated three to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or, a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

wherein said T_{IV} substituent is optionally mono-, di- or tri-substituted independently with halo, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, hydroxy, (C_1-C_6)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6)alkylamino wherein said (C_1-C_6)alkyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy, (C_1-C_6)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6)alkylamino, said (C_1-C_6)alkyl substituent is also optionally substituted with from one to nine fluorines; and

wherein R_{IV-5} and R_{IV-6}, or R_{IV-6} and R_{IV-7}, and/or R_{IV-7} and R_{IV-8} may also be taken together and can form at least one four to eight membered ring that is partially saturated or fully unsaturated optionally having one to three heteroatoms independently selected from nitrogen, sulfur and oxygen;

wherein said ring or rings formed by R_{IV-5} and R_{IV-6}, or R_{IV-6} and R_{IV-7}, and/or R_{IV-7} and R_{IV-8} are optionally mono-, di- or tri-substituted independently with halo, (C_1-C_6)alkyl, (C_1-C_4)alkylsulfonyl, (C_2-C_6)alkenyl, hydroxy, (C_1-C_6)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6)alkylamino wherein said (C_1-C_6)alkyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy, (C_1-C_6) alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6) alkylamino, said (C_1-C_6)alkyl substituent is also optionally substituted with from one to nine fluorines;

with the proviso that when R_{IV-2} is carboxyl or (C_1-C_4)alkylcarboxyl, then R_{IV-1} is not hydrogen.

[0091] Compounds of Formula IV and their methods of manufacture are disclosed in commonly assigned United States Patent No. 6,197,786, United States Application Serial No. 09/685,3000 filed 10/10/00, and PCT Publication No. WO 00/17164, all of which are incorporated herein by reference in their entireties for all purposes.

with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono-, or di-substituted with oxo, and said carbon chain is optionally mono-substituted with Z_V;

wherein Z_V is a partially saturated, fully saturated or fully unsaturated three to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

wherein said Z_V substituent is optionally mono-, di- or tri-substituted independently with halo, (C_2-C_6)alkenyl, (C_1-C_6) alkyl, hydroxy, (C_1-C_6)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6)alkylamino wherein said (C_1-C_6)alkyl substituent is optionally mono-, di- or tri-substituted independently with halo, hydroxy, (C_1-C_6)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_6)alkyloxy-carbonyl, mono-N- or di-N,N-(C_1-C_6)alkylamino, said (C_1-C_6)alkyl substituent is also optionally substituted with from one to nine fluorines;

[0094] R_{V-2} is a partially saturated, fully saturated or fully unsaturated one to six membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one or two heteroatoms selected independently from oxygen, sulfur and nitrogen wherein said carbon atoms are optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with oxo, said carbon is optionally mono-substituted with hydroxy, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with oxo; or said R_{V-2} is a partially saturated, fully saturated or fully unsaturated three to seven membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen,

wherein said R_{V-2} ring is optionally attached through (C_1-C_4)alkyl;

wherein said R_{V-2} ring is optionally mono-, di- or tri-substituted independently with halo, (C_2-C_6)alkenyl, (C_1-C_6) alkyl, hydroxy, (C_1-C_6)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6)alkylamino wherein said (C_1-C_6)alkyl substituent is optionally mono-, di- or tri-substituted independently with halo, hydroxy, (C_1-C_6)alkoxy, (C_1-C_4)alkylthio, oxo or (C_1-C_6)alkyloxycarbonyl;

R_{V-3} is hydrogen or Q_V;

wherein Q_V is a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain wherein the carbons, other than the connecting carbon, may optionally be replaced with one heteroatom selected from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono-, or di-substituted with oxo, and said carbon chain is optionally mono-substituted with V_V;

wherein V_V is a partially saturated, fully saturated or fully unsaturated three to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

wherein said V_V substituent is optionally mono-, di-, tri-, or tetra-substituted independently with halo, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, hydroxy, (C_1-C_6)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxamoyl, mono-N- or di-N, N-(C_1-C_6) alkylcarboxamoyl, carboxy, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6)alkylamino wherein said (C_1-C_6)alkyl or (C_2-C_6)alkenyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy, (C_1-C_6) alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6) alkylamino, said (C_1-C_6)alkyl or (C_2-C_6)alkenyl substituents are also optionally substituted with from one to nine fluorines;

R_{V-4} is cyano, formyl, $W_{V-1}Q_{V-1}$, $W_{V-1}V_{V-1}$, (C_1-C_4)alkyleneV_{V-1} or V_{V-2};

wherein W_{V-1} is carbonyl, thiocarbonyl, SO or SO_2,

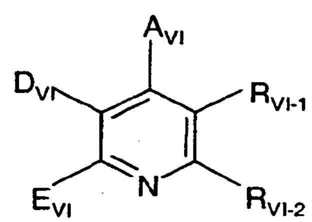
wherein Q_{V-1} a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain wherein the carbons may optionally be replaced with one heteroatom selected from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono-, or di-substituted with oxo, and said carbon chain is optionally mono-substituted with V_{V-1};

wherein V_{V-1} is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

wherein said V_{V-1} substituent is optionally mono-, di-, tri-, or tetra-substituted independently with halo, (C_1-C_6) alkyl, (C_1-C_6)alkoxy, hydroxy, oxo, amino, nitro, cyano, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6)alkylamino

[2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-formyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
[2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-formyl-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
[2S,4S] 4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester;
[2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-formyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
[2S,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-formyl-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;
[2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-formyl-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester; and
[2R,4S] 4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.

[0097] Another class of CETP inhibitors that finds utility with the present invention consists of cycloalkano-pyridines having the Formula VI



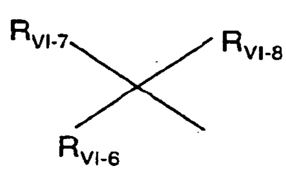
Formula VI

and pharmaceutically acceptable salts, enantiomers, or stereoisomers of said compounds;
in which

[0098] A_{VI} denotes an aryl containing 6 to 10 carbon atoms, which is optionally substituted with up to five identical or different substituents in the form of a halogen, nitro, hydroxyl, trifluoromethyl, trifluoromethoxy or a straight-chain or branched alkyl, acyl, hydroxyalkyl or alkoxy containing up to 7 carbon atoms each, or in the form of a group according to the formula $-BNR_{VI-3}R_{VI-4}$, wherein

[0099] R_{VI-3} and R_{VI-4} are identical or different and denote a hydrogen, phenyl or a straight-chain or branched alkyl containing up to 6 carbon atoms,

[0100] D_{VI} denotes an aryl containing 6 to 10 carbon atoms, which is optionally substituted with a phenyl, nitro, halogen, trifluoromethyl or trifluoromethoxy, or a radical according to the formula $R_{VI-5}-L_{VI}-$,

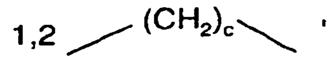


or $R_{VI-9}-T_{VI}-V_{VI}-X_{VI}$, wherein

R_{VI-5}, R_{VI-6} and R_{VI-9} denote, independently from one another, a cycloalkyl containing 3 to 6 carbon atoms, or an aryl containing 6 to 10 carbon atom or a 5- to 7-membered, optionally benzo-condensed, saturated or unsaturated, mono-, bi- or tricyclic heterocycle containing up to 4 heteroatoms from the series of S, N and/or O, wherein the rings are optionally substituted, in the case of the nitrogen-containing rings also via the N function, with up to five identical or different substituents in the form of a halogen, trifluoromethyl, nitro, hydroxyl, cyano, carboxyl, trifluoromethoxy, a straight-chain or branched acyl, alkyl, alkylthio, alkylalkoxy, alkoxy or alkoxycarbonyl containing up to 6 carbon atoms each, an aryl or trifluoromethyl-substituted aryl containing 6 to 10 carbon atoms each, or an optionally benzo-con-

R_{VI-20} and R_{VI-21} are identical or different and denote a hydrogen, phenyl or a straight-chain or branched alkyl containing up to 6 carbon atoms, or

R_{VI-20} and R_{VI-21} together form a 3- to 6-membered carbocyclic ring, and a the carbocyclic rings formed are optionally substituted, optionally also geminally, with up to six identical or different substituents in the form of trifluoromethyl, hydroxyl, nitrile, halogen, carboxyl, nitro, azido, cyano, cycloalkyl or cycloalkyloxy containing 3 to 7 carbon atoms each, a straight-chain or branched alkoxycarbonyl, alkoxy or alkylthio containing up to 6 carbon atoms each, or a straight-chain or branched alkyl containing up to 6 carbon atoms, which is in turn substituted with up to two identical or different substituents in the form of a hydroxyl, benzyloxy, trifluoromethyl, benzoyl, a straight-chain or branched alkoxy, oxyacyl or carboxyl containing up to 4 carbon atoms each and/or a phenyl, which may in turn be substituted with a halogen, trifluoromethyl or trifluoromethoxy, and/or the carbocyclic rings fomed are optionally substituted, also geminally, with up to five identical or different substituents in the form of a phenyl, benzoyl, thiophenyl or sulfonylbenzyl, which in turn are optionally substituted with a halogen, trifluoromethyl, trifluoromethoxy or nitro, and/or optionally in the form of a radical according to the formula



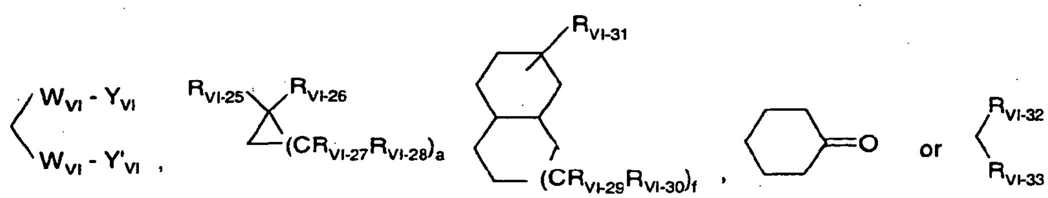
$-SO_2-C_6H_5$, $-(CO)_dNR_{VI-23}R_{VI-24}$ or =O,

wherein

c is a number equaling 1, 2, 3 or 4,

d is a number equaling 0 or 1,

R_{VI-23} and R_{VI-24} are identical or different and denote a hydrogen, cycloalkyl containing 3 to 6 carbon atoms, a straight-chain or branched alkyl containing up to 6 carbon atoms, benzyl or phenyl, which is optionally substituted with up to two identical or different substituents in the form of halogen, trifluoromethyl, cyano, phenyl or nitro, and/or the carbocyclic rings formed are optionally substituted with a spiro-linked radical according to the formula



wherein

W_{VI} denotes either an oxygen atom or a sulfur atom,

Y_{VI} and $Y=_{VI}$ together form a 2- to 6-membered straight-chain or branched alkylene chain,

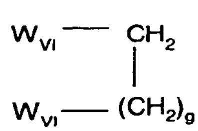
e is a number equaling 1, 2, 3, 4, 5, 6 or 7,

f is a number equaling 1 or 2,

R_{VI-25}, R_{VI-26}, R_{VI-27}, R_{VI-28}, R_{VI-29}, R_{VI-30} and R_{VI-31} are identical or different and denote a hydrogen, trifluoromethyl, phenyl, halogen or a straight-chain or branched alkyl or alkoxy containing up to 6 carbon atoms each, or

R_{VI-25} and R_{VI-26} or R_{VI-27} and R_{VI-28} each together denote a straight-chain or branched alkyl chain containing up to 6 carbon atoms or

R_{VI-25} and R_{VI-26} or R_{VI-27} and R_{VI-28} each together form a radical according to the formula



wherein

W_{VI} has the meaning given above,

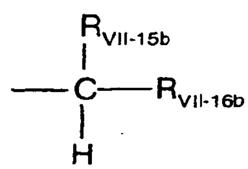
g is a number equaling 1, 2, 3, 4, 5, 6 or 7,

R_{VI-32} and R_{VI-33} together form a 3- to 7-membered heterocycle, which contains an oxygen or sulfur atom or a group according to the formula SO, SO_2 or BNR_{VI-34}, wherein

R_{VI-34} denotes a hydrogen atom, a phenyl, benzyl, or a straight-chain or branched alkyl containing up to 4 carbon

alkyl, heteroarylalkyl, heterocyclylalkyl, cycloalkylalkenyl, cycloalkenylalkenyl, aralkenyl, hetereoarylalkenyl, heterocyclylalkenyl, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, heterocyclyloxy, alkanoyloxy, alkenoyloxy, alkynoyloxy, aryloyloxy, heteroaroyloxy, heterocyclyloyloxy, alkoxycarbonyl, alkenoxycarbonyl, alkynoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, heterocyclyloxycarbonyl, thio, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, alkylthioalkyl, alkenylthioalkyl, alkynylthioalkyl, arylthioalkyl, heteroarylthioalkyl, heterocyclylthioalkyl, alkylthioalkenyl, alkenylthioalkenyl, alkynylthioalkenyl, arylthioalkenyl, heteroarylthioalkenyl, heterocyclythioalkenyl, alkylamino, alkenylamino, alkynylamino, arylamino, heteroarylamino, heterocyclylamino, aryldialkylamino, diarylamino, diheteroarylamino, alkylarylamino, alkylheteroarylamino, arylheteroarylamino, trialkylsilyl, trialkenylsilyl, triarylsilyl,
$-CO(O)N(R_{VII-8a}R_{VII-8b})$, wherein R_{VII-8a} and R_{VII-8b} are independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl, $-SO_2R_{VII-9}$, wherein R_{VII-9} is selected from the group consisting of hydroxy, alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl, $-OP(O)(OR_{VII-10a})(OR_{VII-10b})$, wherein $R_{VII-10a}$ and $R_{VII-10b}$ are independently selected from the group consisting of hydrogen, hydroxy, alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl, and $-OP(S)(OR_{VII-11a})(OR_{VII-11b})$, wherein $R_{VII-11a}$ and $R_{VII-11b}$ are independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl;

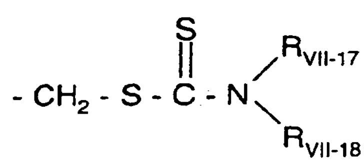
R_{VII-5} is selected from the group consisting of hydrogen, hydroxy, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, haloalkyl, haloalkenyl, haloalkynyl, aryl, heteroaryl, heterocyclyl, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, heterocyclyloxy, alkylcarbonyloxyalkyl, alkenylcarbonyloxyalkyl, alkynylcarbonyloxyalkyl, arylcarbonyloxyalkyl, heteroarylcarbonyloxyalkyl, heterocyclylcarbonyloxyalkyl, cycloalkylalkyl, cycloalkenylalkyl, aralkyl, heteroarylalkyl, heterocyclylalkyl, cycloalkylalkenyl, cycloalkenylalkenyl, aralkenyl, heteroarylalkenyl, heterocyclylalkenyl, alkylthioalkyl, cycloalkylthioalkyl, alkenylthioalkyl, alkynylthioalkyl, arylthioalkyl, heteroarylthioalkyl, heterocyclylthioalkyl, alkylthioalkenyl, alkenylthioalkenyl, alkynylthioalkenyl, arylthioalkenyl, heteroarylthioalkenyl, heterocyclylthioalkenyl, alkoxyalkyl, alkenoxyalkyl, alkynoxylalkyl, aryloxyalkyl, heteroaryloxyalkyl, heterocyclyloxyalkyl, alkoxyalkenyl, alkenoxyalkenyl, alkynoxyalkenyl, aryloxyalkenyl, heteroaryloxyalkenyl, heterocyclyloxyalkenyl, cyano, hydroxymethyl, $-CO_2R_{VII-14}$, wherein R_{VII-14} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl;



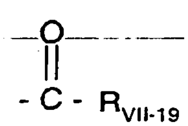
,

wherein $R_{VII-15b}$ is selected from the group consisting of hydroxy, hydrogen, halogen, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio, heterocyclylthio, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, heterocyclyloxy, aroyloxy, and alkylsulfonyloxy, and

$R_{VII-16b}$ is selected form the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkoxy, and trialkylsilyloxy;



wherein R_{VII-17} and R_{VII-18} are independently selected from the group consisting of alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl;



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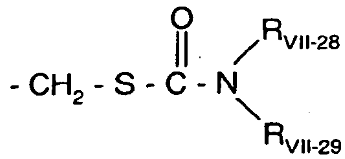
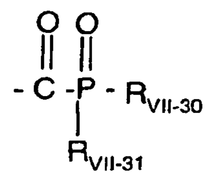
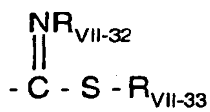


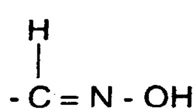
wherein R_{VII-28} and R_{VII-29} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;



wherein R_{VII-30} and R_{VII-31} are independently alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, and heterocyclyloxy; and

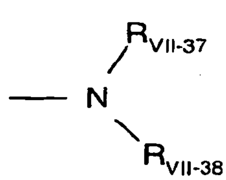


wherein R_{VII-32} and R_{VII-33} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;



$$C \equiv C - SI(R_{VII-36})_3,$$

wherein R_{VII-36} is selected from the group consisting of alkyl, alkenyl, aryl, heteroaryl and heterocyclyl;



wherein R_{VII-37} and R_{VII-38} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;

cyclylthioalkyl, alkylthioalkenyl, alkenylthioalkenyl, alkynylthioalkenyl, arylthioalkenyl, heteroarylthioalkenyl, heterocyclylthioalkenyl, aminocarbonylalkyl, aminocarbonylalkenyl, aminocarbonylalkynyl, aminocarbonylaryl, aminocarbonylheteroaryl, and aminocarbonylheterocyclyl,

$$-SR_{VII-46}, \text{ and } -CH_2R_{VII-47},$$

wherein R_{VII-46} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl, and

R_{VII-47} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl; and

$$-S-CH\begin{array}{l} \diagup R_{VII-48} \\ \diagdown R_{VII-49} \end{array},$$

wherein R_{VII-48} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl, and

R_{VII-49} is selected from the group consisting of alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, heterocyclyloxy, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl and haloheterocyclyl;

$$-S-\overset{\overset{\displaystyle O}{\|}}{C}-R_{VII-50},$$

wherein R_{VII-50} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy and heterocyclyloxy;

$$-\overset{\overset{\displaystyle O}{\|}}{S}-R_{VII-51},$$

wherein R_{VII-51} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl and haloheterocyclyl; and

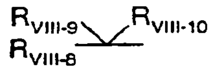
$$-\underset{\underset{\displaystyle O}{\|}}{\overset{\overset{\displaystyle O}{\|}}{S}}-R_{VII-53},$$

wherein R_{VII-53} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl;

provided that when R_{VII-5} is selected from the group consisting of heterocyclylalkyl and heterocyclylalkenyl, the heterocyclyl radical of the corresponding heterocyclylalkyl or heterocyclylalkenyl is other than δ-lactone; and

provided that when R_{VII-4} is aryl, heteroaryl or heterocyclyl, and one of R_{VII-2} and R_{VII-6} is trifluoromethyl, then the other of R_{VII-2} and R_{VII-6} is difluoromethyl.

[0104] Compounds of Formula VII and their methods of manufacture are disclosed in PCT Publication No. WO 9941237-A1, which is incorporated herein by reference in its entirety for all purposes.

R_{VIII-7} - X_{VIII} - or  wherein

R_{VIII-7} and R_{VIII-8} are identical or different and denote cycloalkyl with 3 to 8 carbon atoms, or aryl with 6 to 10 carbon atoms, or denote a 5- to 7-member aromatic, optionally benzo-condensed, heterocyclic compound with up to 3 heteroatoms from the series S, N and/or O, which are optionally substituted up to 3 times in an identical manner or differently by trifluoromethyl, trifluoromethoxy, halogen, hydroxy, carboxyl, by straight-chain or branched alkyl, acyl, alkoxy, or alkoxycarbonyl with up to 6 carbon atoms each, or by phenyl, phenoxy, or thiophenyl, which can in turn be substituted by halogen, trifluoromethyl, or trifluoromethoxy, and/or the rings are substituted by a group of the formula

$$-NR_{VIII-11}R_{VIII-12},$$

wherein

$R_{VIII-11}$ and $R_{VIII-12}$ are identical or different and have the meaning given above for R_{VIII-1} and R_{VIII-2},

X_{VIII} denotes a straight or branched alkyl chain or alkenyl chain with 2 to 10 carbon atoms each, which are optionally substituted up to 2 times by hydroxy,

R_{VIII-9} denotes hydrogen, and

$R_{VIII-10}$ denotes hydrogen, halogen, azido, trifluoromethyl, hydroxy, mercapto, trifluoromethoxy, straight-chain or branched alkoxy with up to 5 carbon atoms, or a radical of the formula

$$-NR_{VIII-13}R_{VIII-14},$$

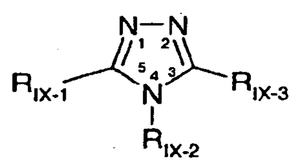
wherein

$R_{VIII-13}$ and $R_{VIII-14}$ are identical or different and have the meaning given above for R_{VIII-1} and R_{VIII-2}, or

R_{VIII-9} and $R_{VIII-10}$ form a carbonyl group together with the carbon atom.

Compounds of Formula VIII are disclosed in PCT Publication No. WO 9804528, which is incorporated herein by reference in its entirety for all purposes.

[0107] Another class of CETP inhibitors that finds utility with the present invention consists of substituted 1,2,4-triazoles having the Formula IX



Formula IX

or a pharmaceutically acceptable salt or tautomer thereof;

wherein R_{IX-1} is selected from higher alkyl, higher alkenyl, higher alkynyl, aryl, aralkyl, aryloxyalkyl, alkoxyalkyl, alkylthioalkyl, arylthioalkyl, and cycloalkylalkyl;

wherein R_{IX-2} is selected from aryl, heteroaryl, cycloalkyl, and cycloalkenyl,

wherein

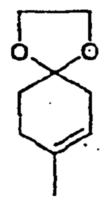
R_{IX-2} is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, haloalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxy, halo, aryloxy, aralkyloxy, aryl, aralkyl, aminosulfonyl, amino, monoalkylamino and dialkylamino; and

wherein R_{IX-3} is selected from hydrido, -SH and halo;

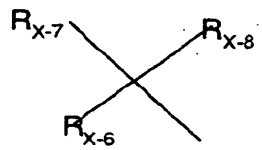
provided R_{IX-2} cannot be phenyl or 4-methylphenyl when R_{IX-1} is higher alkyl and when R_{IX-3} is BSH.

[0108] Compounds of Formula IX and their methods of manufacture are disclosed in PCT Publication No. WO 9914204, which is incorporated herein by reference in its entirety for all purposes.

[0109] In a preferred embodiment, the CETP inhibitor is selected from the following compounds of Formula IX:



[0111] D_X represents an aryl having 6 to 10 carbon atoms, that is optionally substituted by phenyl, nitro, halogen, trifluormethyl or trifluormethoxy, or it represents a radical of the formula



R_{X-5} — L_X— , or R_{X-9} — T_X — V_X — X_X

in which

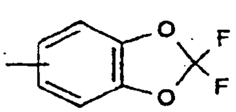
R_{X-5}, R_{X-6} and R_{X-9} independently of one another denote cycloalkyl having 3 to 6 carbon atoms, or an aryl having 6 to 10 carbon atoms or a 5- to 7-membered aromatic, optionally benzo-condensed saturated or unsaturated, mono-, bi-, or tricyclic heterocyclic ring from the series consisting of S, N and/or O, in which the rings are substituted, optionally, in case of the nitrogen containing aromatic rings via the N function, with up to 5 identical or different substituents in the form of halogen, trifluoromethyl, nitro, hydroxy, cyano, carbonyl, trifluoromethoxy, straight straight-chain or branched acyl, alkyl, alkylthio, alkylalkoxy, alkoxy, or alkoxycarbonyl each having up to 6 carbon atoms, by aryl or trifluoromethyl-substituted aryl each having 6 to 10 carbon atoms or by an, optionally benzo-condensed, aromatic 5- to 7-membered heterocyclic ring having up to 3 heteroatoms from the series consisting of S, N, and/or O, and/or substituted by a group of the formula BOR_{X-10}, $-SR_{X-11}$, SO_2R_{X-12} or $BNR_{X-13}R_{X-14}$, in which

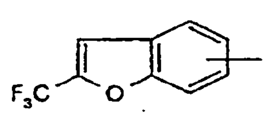
R_{X-10}, R_{X-11} and R_{X-12} independently from each other denote aryl having 6 to 10 carbon atoms, which is in turn substituted with up to 2 identical or different substituents in the form of phenyl, halogen or a straight-chain or branched alkyl having up to 6 carbon atoms,

R_{X-13} and R_{X-14} are identical or different and have the meaning of R_{X-3} and R_{X-4} indicated above,

or

R_{X-5} and/or R_{X-6} denote a radical of the formula





or

R_{X-7} denotes hydrogen or halogen, and

R_{X-8} denotes hydrogen, halogen, azido, trifluoromethyl, hydroxy, trifluoromethoxy, straight-chain or branched alkoxy or alkyl having up to 6 carbon atoms or a radical of the formula

$BNR_{X-15}R_{X-16}$,

in which

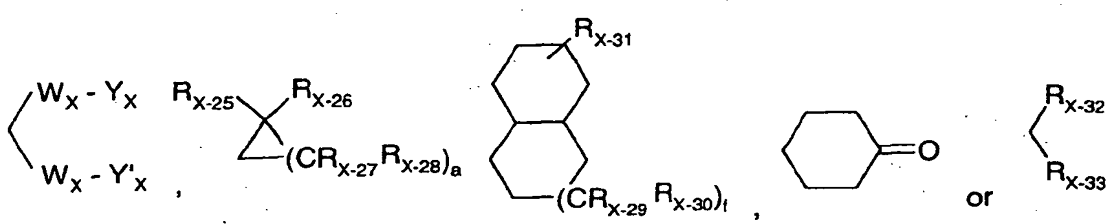
R_{X-15} and R_{X-16} are identical or different and have the meaning of R_{X-3} and R_{X-4} indicated above,

or

R_{X-7} and R_{X-8} together form a radical of the formula =O or $=NR_{X-17}$, in which

d denotes a number equaling 0 or 1,

R_{X-23} and R_{X-24} are identical or different and denote hydrogen, cycloalkyl with 3 to 6 carbon atoms, straight chain or branched alkyl with up to 6 carbon atoms, benzyl or phenyl, that is optionally substituted with up to 2 identically or differently by halogen, trifluoromethyl, cyano, phenyl or nitro, and/or the formed carbocyclic rings are substituted optionally by a spiro-linked radical with the formula



in which

W_X denotes either an oxygen or a sulfur atom

Y_X and Y'_X together form a 2 to 6 membered straight chain or branched alkylene chain,

e denotes a number equaling 1, 2, 3, 4, 5, 6, or 7,

f denotes a number equaling 1 or 2,

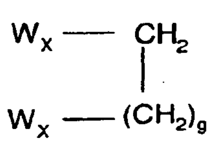
R_{X-25}, R_{X-26}, R_{X-27}, R_{X-28}, R_{X-29}, R_{X-30} and R_{X-31} are identical or different and denote hydrogen, trifluoromethyl, phenyl, halogen or straight chain or branched alkyl or alkoxy with up to 6 carbon atoms each,

or

R_{X-25} and R_{X-26} or R_{X-27} and R_{X-28} respectively form together a straight chain or branched alkyl chain with up to 6 carbon atoms,

or

R_{X-25} and R_{X-26} or R_{X-27} and R_{X-28} each together form a radical with the formula



in which

W_x has the meaning given above, g denotes a number equaling 1, 2, 3, 4, 5, 6, or 7,

R_{X-32} and R_{X-33} form together a 3- to 7- membered heterocycle, which contains an oxygen or sulfur atom or a group with the formula SO, SO_2 or - NR_{X-34},

in which

R_{X-34} denotes hydrogen, phenyl, benzyl or straight or branched alkyl with up to 4 carbon atoms.

[0112] Compounds of Formula X and their methods of manufacture are disclosed in PCT Publication No. WO 9914215, which is incorporated herein by reference in its entirety for all purposes.

[0113] In a preferred embodiment, the CETP inhibitor is selected from the following compounds of Formula X:

2-cyclopentyl-5-hydroxy-7,7-dimethyl-4-(3-thienyl)-3-(4-trifluoromethylbenxoyl)-5,6,7,8-tetrahydroquinoline;
2-cyclopentyl-3-[fluoro-(4-trifluoromethylphenyl)methyl]-5-hydroxy-7,7-dimethyl-4-(3-thienyl)-5,6,7,8-tetrahydroquinoline; and
2-cyclopentyl-5-hydroxy-7,7-dimethyl-4-(3-thienyl)-3-(trifluoromethylbenxyl)-5,6,7,8-tetrahydroquinoline.

[0114] Another class of CETP inhibitors that finds utility with the present invention consists of substituted tetrahydro naphthalines and analogous compound having the Formula XI

R_{XI-7} denotes hydrogen, halogen or methyl,

and

R_{XI-8} denotes hydrogen, halogen, azido, trifluoromethyl, hydroxy, trifluoromethoxy, straight-chain or branched alkoxy or alkyl with up to 6 carbon atoms each, or a radical of the formula $-NR_{XI-15}R_{XI-16}$,

in which

R_{XI-15} and R_{XI-16} are identical or different and have the meaning given above for R_{XI-3} and R_{XI-4},

or

R_{XI-7} and R_{XI-8} together form a radical of the formula =O or $=NR_{XI-17}$, in which

R_{XI-17} denotes hydrogen or straight-chain or branched alkyl, alkoxy or acyl with up to 6 carbon atoms each,

L_{XI} denotes a straight-chain or branched alkylene- or alkenylene chain with up to 8 carbon atoms each, which is possibly substituted up to 2-fold by hydroxy,

T_{XI} and X_{XI} are identical or different and denote a straight-chain or branched alkylene chain with up to 8 carbon atoms,

or

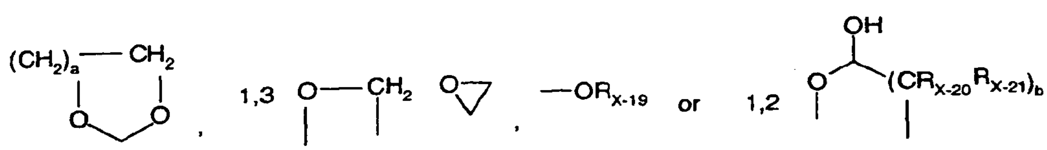
T_{XI} and X_{XI} denotes a bond,

V_{XI} stands for an oxygen- or sulfur atom or for an $-NR_{XI-18}$ group, in which

R_{XI-18} denotes hydrogen or straight-chain or branched alkyl with up to 6 carbon atoms, or phenyl,

E_{XI} stands for cycloalkyl with 3 to 8 carbon atoms, or stands for straight-chain or branched alkyl with up to 8 carbon atoms, which is possibly substituted by cycloalkyl with 3 to 8 carbon atoms or hydroxy, or stands for phenyl, which is possibly substituted by halogen or trifluoromethyl,

R_{XI-1} and R_{XI-2} together form a straight-chain or branched alkylene chain with up to 7 carbon atoms, which must be substituted by a carbonyl group and/or by a radical of the formula



in which

a and b are identical or different and denote a number 1, 2 or 3

R_{XI-19} denotes hydrogen, cycloalkyl with 3 to 7 carbon atoms, straight-chain or branched silylalkyl with up to 8 carbon atoms, or straight-chain or branched alkyl with up to 8 carbon atoms, which is possibly substituted by hydroxy, straight-chain or branched alkoxy with up to 6 carbon atoms, or by phenyl, which itself can be substituted by halogen, nitro, trifluoromethyl, trifluoromethoxy or by phenyl substituted by phenyl or tetrazol, and alkyl is possibly substituted by a group of the formula $-OR_{XI-22}$,

in which

R_{XI-22} denotes straight-chain or branched acyl with up to 4 carbon atoms, or benzyl,

or

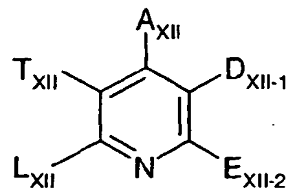
R_{XI-19} denotes straight-chain or branched acyl with up to 20 carbon atoms or benzoyl, which is possibly substituted by halogen, trifluoromethyl, nitro or trifluoromethoxy, or denotes straight-chain or branched fluoroacyl with up to 8 carbon atoms and 9 fluorine atoms,

R_{XI-20} and R_{XI-21} are identical or different, denoting hydrogen, phenyl or straight-chain or branched alkyl with up to 6 carbon atoms,

or

R_{XI-20} and R_{XI-21} together form a 3- to 6-membered carbocycle, and, possibly also geminally, the alkylene chain formed by R_{XI-1} and R_{XI-2}, is possibly substituted up to 6-fold, identical or different, by trifluoromethyl, hydroxy, nitrile, halogen, carboxyl, nitro, azido, cyano, cycloalkyl or cycloalkyloxy with 3 to 7 carbon atoms each, by straight-chain or branched alkoxycarbonyl, alkoxy or alkoxythio with up to 6 carbon atoms each, or by straight- chain or branched alkyl with up to 6 carbon atoms, which itself is substituted up to 2-fold,

identical or different, by hydroxyl, benzyloxy, trifluoromethyl, benzoyl, straight-chain or branched alkoxy, oxyacyl or carboxyl with up to 4 carbon atoms each, and/or phenyl- which itself can be substituted by halogen, trifluoromethyl or trifluoromethoxy, and/or the alkylene chain formed by R_{XI-1} and R_{XI-2} is substituted, also geminally, possibly up to 5-fold, identical or different, by phenyl, benzoyl, thiophenyl or sulfobenzyl -which themselves are possibly substituted by halogen, trifluoromethyl, trifluoromethoxy or nitro, and/or the alkylene chain formed by R_{XI-1} and R_{XI-2} is possibly substituted by a radical of the formula



Formula XII

or pharmaceutically acceptable salts, enantiomers, or stereoisomers of said compounds, in which

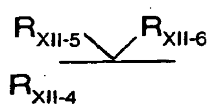
[0117] A_{XII} and E_{XII} are identical or different and stand for aryl with 6 to 10 carbon atoms which is possibly substituted, up to 5-fold identical or different, by halogen, hydroxy, trifluoromethyl, trifluoromethoxy, nitro or by straight-chain or branched alkyl, acyl, hydroxy alkyl or alkoxy with up to 7 carbon atoms each, or by a group of the formula $-NR_{XII-1}R_{XII-2}$, where

R_{XII-1} and R_{XII-2} are identical or different and are meant to be hydrogen, phenyl or straight-chain or branched alkyl with up to 6 carbon atoms,

D_{XII} stands for straight-chain or branched alkyl with up to 8 carbon atoms, which is substituted by hydroxy,

L_{XII} stands for cycloalkyl with 3 to 8 carbon atoms or for straight-chain or branched alkyl with up to 8 carbon atoms, which is possibly substituted by cycloalkyl with 3 to 8 carbon atoms, or by hydroxy,

T_{XII} stands for a radical of the formula $R_{XII-3}-X_{XII}-$ or



where

R_{XII-3} and R_{XII-4} are identical or different and are meant to be cycloalkyl with 3 to 8 carbon atoms, or aryl with 6 to 10 carbon atoms, or a 5- to 7-membered aromatic, possibly benzocondensated heterocycle with up to 3 heteroatoms from the series S, N and/or O, which are possibly substituted. up to 3-fold identical or different, by trifluoromethyl, trifluoromethoxy, halogen, hydroxy, carboxyl, nitro, by straight-chain or branched alkyl, acyl, alkoxy or alkoxycarbonyl with up to 6 carbon atoms each. or by phenyl, phenoxy or phenylthio which in turn can be substituted by halogen, trifluoromethyl or trifluoromethoxy, and/or where the cycles are possibly substituted by a group of the formula $-NR_{XII-7}R_{XII-8}$,

where

R_{XII-7} and R_{XII-8} are identical or different and have the meaning of R_{XII-1} and R_{XII-2} given above,

X_{XII} is a straight-chain or branched alkyl or alkenyl with 2 to 10 carbon atoms each, possibly substituted up to 2-fold by hydroxy or halogen,

R_{XII-5} stands for hydrogen,

and

[0118] R_{XII-6} means to be hydrogen, halogen, mercapto, azido, trifluoromethyl, hydroxy, trifluoromethoxy, straight-chain or branched alkoxy with up to 5 carbon atoms, or a radical of the formula $BNR_{XII-9}R_{XII-10}$,

where

R_{XII-9} and R_{XII-10} are identical or different and have the meaning of R_{XII-1} and R_{XII-2} given above,

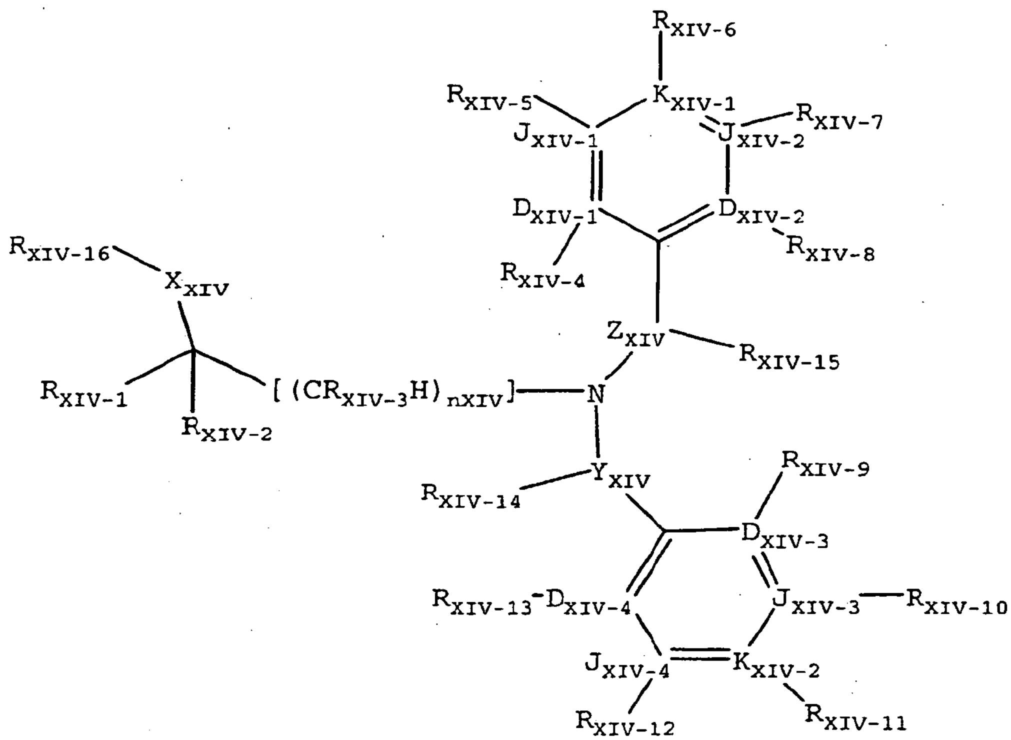
or

R_{XII-5} and R_{XII-6}, together with the carbon atom, form a carbonyl group.

Compounds of Formula XII and their methods of manufacture are disclosed in EP 796846-A1, United States Patent No. 6,127,383 and United States Patent No. 5,925,645, all of which are incorporated herein by reference in their entireties for all purposes.

[0119] In a preferred embodiment, the CETP inhibitor is selected from the following compounds of Formula XII:

4,6-bis-(p-fluorophenyl)-2-isopropyl-3-[(p-trifluoromethylphenyl)-(fluoro)-methyl]-5-(1-hydroxyethyl)pyridine;



Formula XIV

and pharmaceutically acceptable forms thereof, wherein:

n_{XIV} is an integer selected from 0 through 5;

R_{XIV-1} is selected from the group consisting of haloalkyl, haloalkenyl, haloalkoxyalkyl, and haloalkenyloxyalkyl;

X_{XIV} is selected from the group consisting of O, H, F, S, S(O),NH, N(OH), N(alkyl), and N(alkoxy);

R_{XIV-16} is selected from the group consisting of hydrido, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, alkoxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, aralkoxyalkyl, heteroaralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, cycloalkyl, cycloalkylalkyl,
cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl, monocarboalkoxyalkyl, monocarboalkoxy, dicarboalkoxyalkyl, monocarboxamido, monocyanoalkyl, dicyanoalkyl, carboalkoxycyanoalkyl, acyl, aroyl, heteroaroyl,
heteroaryloxyalkyl, dialkoxyphosphonoalkyl, trialkylsilyl, and a spacer selected from the group consisting of a covalent single bond and a linear spacer moiety having from 1 through 4 contiguous atoms linked to the point of bonding of an aromatic substituent selected from the group consisting of R_{XIV-4}, R_{XIV-8}, R_{XIV-9}, and R_{XIV-13} to form a heterocyclyl ring having from 5 through 10 contiguous members with the provisos that said spacer moiety is other than a covalent single bond when R_{XIV-2} is alkyl and there is no R_{XIV-16} wherein X is H or F;

D_{XIV-1}, D_{XIV-2}, J_{XIV-1}, J_{XIV-2} and K_{XIV-1} are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one of D_{XIV-1}, D_{XIV-2}, J_{XIV-1}, J_{XIV-2} and K_{XIV-1} is a covalent bond, no more than one of D_{XIV-1}, D_{XIV-2}, J_{XIV-1}, J_{XIV-2} and K_{XIV-1} is O, no more than one of D_{XIV-1}, D_{XIV-2}, J_{XIV-1}, J_{XIV-2} and K_{XIV-1} is S, one of D_{XIV-1}, D_{XIV-2}, J_{XIV-1}, J_{XIV-2} and K_{XIV-1} must be a covalent bond when two of D_{XIV-1}, D_{XIV-2}, J_{XIV-1}, J_{XIV-2} and K_{XIV-1} are O and S, and no more than four of D_{XIV-1}, D_{XIV-2}, J_{XIV-1}, J_{XIV-2} and K_{XIV-1} are N;

D_{XIV-3}, D_{XIV-4}, J_{XIV-3}, J_{XIV-4} and K_{XIV-2} are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one of D_{XIV-3}, D_{XIV-4}, J_{XIV-3}, J_{XIV-4} and K_{XIV-2} is a covalent bond, no more than one of D_{XIV-3}, D_{XIV-4}, J_{XIV-3}, J_{XIV-4} and K_{XIV-2} is O, no more than one of D_{XIV-3}, D_{XIV-4}, J_{XIV-3}, J_{XIV-4} and K_{XIV-2}

having from 5 through 8 contiguous members;

R_{XIV-14} and R_{XIV-14}, when bonded to the same atom are taken together to form a group selected from the group consisting of oxo, thiono, alkylene, haloalkylene, and a spacer selected from the group consisting of a moiety having a chain length of 3 to 7 atoms connected to form a ring selected from the group consisting of a cycloalkyl having from 4 through 8 contiguous members, a cycloalkenyl having from 4 through 8 contiguous members, and a heterocyclyl having from 4 through 8 contiguous members;

W_{XIV} is selected from the group consisting of O, C(O), C(S), C(O)N(R_{XIV-14}), C(S)N(R_{XIV-14}), (R_{XIV-14})NC(O), (R_{XIV-14})NC(S), S, S(O), $S(O)_2$, $S(O)_2N(R_{XIV-14})$, (R_{XIV-14})$NS(O)_2$, and N(R_{XIV-14}) with the proviso that R_{XIV-14} is selected from other than halo and cyano;

Z_{XIV} is independently selected from a group consisting of a covalent single bond, $(C(R_{XIV-15})_2)_{qXIV-2}$ wherein $_{qXIV-2}$ is an integer selected from 1 and 2, $(CH(R_{XIV-15}))_{jXIV}$-W-$(CH(R_{XIV-15}))_{kXIV}$ wherein $_{jXIV}$ and $_{kXIV}$ are integers independently selected from 0 and 1 with the proviso that, when Z_{XIV} is a covalent single bond, an R_{XIV-15} substituent is not attached to Z_{XIV};

R_{XIV-15} is independently selected, when Z_{XIV} is $(C(R_{XIV-15})_2)_{qXIV}$ wherein $_{qXIV}$ is an integer selected from 1 and 2, from the group consisting of hydrido, hydroxy, halo, cyano, aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, acyl, aroyl, heteroaroyl, heteroaryloxyalkyl, sulfhydryl, acylamido, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkylthioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl, heteroarylthioalkyl, heteroaralkylthioalkyl, monocarboalkoxyalkyl, dicarboalkoxyalkyl, monocyanoalkyl, dicyanoalkyl, carboalkoxycyanoalkyl, alkylsulfinyl, alkylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, arylsulfonylalkyl, aralkylsulfinyl, aralkylsulfonyl, cycloalkylsulfinyl, cycloalkylsulfonyl, cycloalkylsulfinylalkyl, cycloalkylsufonylalkyl, heteroarylsulfonylalkyl, heteroarylsulfinyl, heteroarylsulfonyl, heteroarylsulfinylalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxy, carboxyalkyl, carboalkoxy, carboxamide, carboxamidoalkyl, carboaralkoxy, dialkoxyphosphono, diaralkoxyphosphono, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, a spacer selected from a moiety having a chain length of 3 to 6 atoms connected to the point of bonding selected from the group consisting of R_{XIV-4} and R_{XIV-8} to form a ring selected from the group consisting of a cycloalkenyl ring having from 5 through 8 contiguous members and a heterocyclyl ring having from 5 through 8 contiguous members, and a spacer selected from a moiety having a chain length of 2 to 5 atoms connected to the point of bonding selected from the group consisting of R_{XIV-9} and R_{XIV-13} to form a heterocyclyl having from 5 through 8 contiguous members;

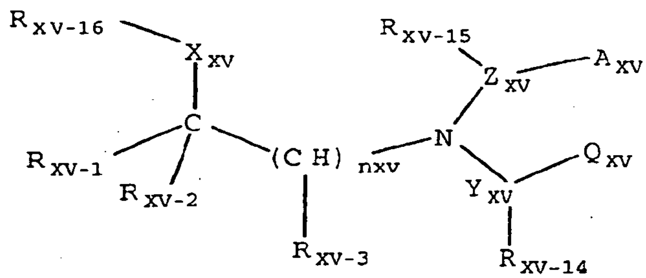
R_{XIV-15} and R_{XIV-15}, when bonded to the different atoms, are taken together to form a group selected from the group consisting of a covalent bond, alkylene, haloalkylene, and a spacer selected from a group consisting of a moiety having a chain length of 2 to 5 atoms connected to form a ring selected from the group of a saturated cycloalkyl having from 5 through 8 contiguous members, a cycloalkenyl having from 5 through 8 contiguous members, and a heterocyclyl having from 5 through 8 contiguous members;

R_{XIV-15} and R_{XIV-15}, when bonded to the same atom are taken together to form a group selected from the group consisting of oxo, thiono, alkylene, haloalkylene, and a spacer selected from the group consisting of a moiety having a chain length of 3 to 7 atoms connected to form a ring selected from the group consisting of a cycloalkyl having from 4 through 8 contiguous members, a cycloalkenyl having from 4 through 8 contiguous members, and a heterocyclyl having from 4 through 8 contiguous members;

R_{XIV-15} is independently selected, when Z_{XIV} is $(CH(R_{XIV-15}))_{jXIV}$-W-$(CH(R_{XIV-15}))_{kXIV}$ wherein $_{jXIV}$ and $_{kXIV}$ are integers independently selected from 0 and 1, from the group consisting of hydrido, halo, cyano, aryloxy, carboxyl, acyl, aroyl, heteroaroyl, hydroxyalkyl, heteroaryloxyalkyl, acylamido, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, alkoxyalkyl, heteroaryloxyalkyl, aralkoxyalkyl, heteroaralkoxyalkyl, alkylsulfonylalkyl, alkylsulfinylalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl, heteroarylthioalkyl, heteroaralkylthioalkyl, monocarboalkoxyalkyl, dicarboalkoxyalkyl, monocyanoalkyl, dicyanoalkyl, carboalkoxycyanoalkyl, alkylsulfinyl, alkylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, arylsulfonylalkyl, aralkylsulfinyl, aralkylsulfonyl, cycloalkylsulfinyl, cycloalkylsulfonyl, cycloalkylsulfinylalkyl, cycloalkylsufonylalkyl, heteroarylsulfonylalkyl, heteroarylsulfinyl, heteroarylsulfonyl, heteroarylsulfinylalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxyalkyl, carboalkoxy, carboxamide, carboxamidoalkyl, carboaralkoxy, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, a spacer selected from a linear moiety having a chain length of 3 to 6 atoms connected to the point of bonding selected from the group consisting of R_{XIV-4} and R_{XIV-8} to form a ring selected from the group consisting of a cycloalkenyl ring having from 5 through 8 contiguous members and a heterocyclyl ring having from 5 through 8 contiguous members,

nol;
3-[[3-(4-fluorophenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(4-methlylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(2-fluoro-5-bromophenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1 -trifluoro-2-propanol;
3-[[3-(4-chloro-3-ethylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-[3-(1,1,2,2- tetrafluoroethoxy)phenoxy]phenyl][[3-(1,1,2,2-tetrafluoro-ethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-[3-(pentafluoroethyl)phenoxy]phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3,5-dimethylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-ethylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy) phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-t-butylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]1,1,1-trifluoro-2-propanol;
3-[[3-(3-methylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(5,6,7,8-tetrahydro-2-naphthoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(phenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-[3-(N,N-dimethylamino)phenoxy]phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methy1][3-[[3-(trifluoromethoxy)-phenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanoi;
3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3-[[3-(trifluoromethyl)-phenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3-[[3,5-dimethylphenyl]-methoxy]phenyl]amino]-1,1,1 -trifluoro-2-propanol;
3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3-[[3-(trifluoromethylthio)-phenyl]methoxy]phenyl]amino]-1,1,-trifluoro-2-propanol;
3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3-[[3,5-difluorophenyl]-methoxy]phenyl]amino]-1,1,1 -trifluoro-2-propanol;
3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3-[cyclohexylmethoxy]-phenyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(2-difluoromethoxy-4-pyridyloxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(2-trifluoromethyl-4-pyridyloxy)phenyl][[3-(1,1,2,2- tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-difluoromethoxyphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[[3-(3-trifluoromethylthio)phenoxy]phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(4-chloro-3-trifluoromethylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1,-trifluoro-2-propanol;
3-[[3-(3-trifluoromethoxyphenoxy)phenyl][[3-(pentafluoroethymethyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-isopropylphenoxy)phenyl][[3-(pentafluoroethyl) phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-cyclopropylphenoxy)phenyl][[3-(pentafluoroethyl) phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-(2-furyl)phenoxy)phenyl][[3-(pentafluoroethyl)phenyl]methyl]-amino]-1,1,1 -trifluoro-2-propanol;
3-[[3-(2,3-dichlorophenoxy)phenyl][[3-(pentafluoroethyl) phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(4-fluorophenoxy)phenyl][[3-(pentafluoroethyl) phenyl]methyl]amino]-1,1,1 -trifluoro-2-propanol;
3-[[3-(4-methylphenoxy)phenyl][[3-(pentafluoroethyl) phenyl]methyl]amino]-1,1,1 -trifluoro-2-propanol;
3-[[3-(2-fluoro-5-bromophenoxy)phenyl][[3-(pentafluoroethyl) phenyl]methyl]-amino]-1,1,1 -trifluoro-2-propanol;
3-[[3-(4-chloro-3-ethylphenoxy)phenyl][[3-(pentafluoroethyl) phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
3-[[3-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl][[3-(pentafluoroethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-[3-(pentafluoroethyl)phenoxy]phenyl][[3-(pentafluoroethyl)phenyl]-methyl]amino]-1,1,1 -trifluoro-2-propanol;
3-[[3-(3,5-dimethylphenoxy)phenyl][[3-(pentafluoroethyl) phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-ethylphenoxy)phenyl][[3-(pentafluoroethyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-t-butylphenoxy)phenyl][[3-(pentafluoroethyl) phenyl]methyl]amino]-1,1,1 -trifluoro-2-propanol;
3-[[3-(3-methylphenoxy)phenyl][[3-pentafluoroethyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;

3-[[3-(2-trifluoromethyl-4-pyridyloxy)phenyl][[3-(heptafluoropropyl)phenyl]-methyl]amino]-1,1,1 -trifluoro-2-propanol;
3-[[3-(3-difluoromethoxyphenoxy)phenyl][[3-(heptafluoropropyl) phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[[3-(3-trifluoromethylthio)phenoxy]phenyl][[3-(heptafluoropropyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(4-chloro-3-trifluoromethylphenoxy)phenyl][[3-(heptafluoropropyl)-phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-trifluoromethoxyphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)-phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-isopropylphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-cyclopropylphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-(2-furyl)phenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(2,3-dichlorophenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1 -trifluoro-2-propanol;
3-[[3-(4-fluorophenoxy)phenyl][[2-fluoro-5-(trifluoromethyl) phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(4-methylphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(2-fluoro-5-bromophenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(4-chloro-3-ethylphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-[3-(pentafluoroethyl)phenoxy]phenyl][[2-fluoro-5-(trifluoromethyl)-phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3,5-dimethylphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-ethylphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl) phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-t-butylphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl) phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-methylphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl) phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(5,6,7,8-tetrahydro-2-naphthoxy)phenyl][[2-fluoro-5-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(phenoxy)phenyl][[2-fluoro-5-(trifluoromethyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-[3-(N,N-dimethylamino)phenoxy]phenyl][[2-fluoro-5-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[[2-fluoro-5-(trifluoromethyl)phenyl]methyl][3-[[3-(trifluoromethoxy)-phenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[[2-fluoro-5-(trifluoromethyl)phenyl]methyl][3-[[3-(trifluoromethyl)-phenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[[2-fluoro-5-(trifluoromethyl)phenyl]methyl][3-[[3,5-dimethylphenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[[2-fluoro-5-(trifluoromethyl)phenyl]methyl][3-[[3-(trifluoromethylthio)-phenyl]methoxy]phenyl]amino]-1,1,1 -trifluoro-2-propanol;
3-[[[2-fluoro-5-(trifluoromethyl)phenyl]methyl][3-[[3,5-difluorophenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[[2-fluoro-5-(trifluoromethyl)phenyl]methyl][3-[cyclohexylmethoxy]-phenyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(2-difluoromethoxy-4-pyridyloxy)phenyl][[2-fluoro-5-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(2-trifluoromethyl-4-pyridyloxy)phenyl][[2-fluoro-5-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-difluoromethoxyphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[[3-(3-trifluoromethylthio)phenoxy]phenyl][[2-fluoro-5-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(4-chloro-3-trifluoromethylphenoxy)phenyl][[2-fluoro-5-(trifluoromethyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-trifluoromethoxyphenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-isopropylphenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-cyclopropylphenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1 -trifluoro-2-propanol;



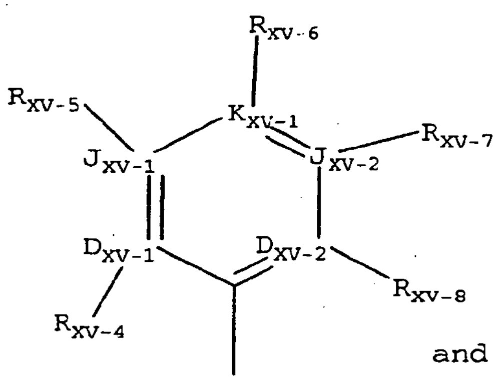
Formula XV

and pharmaceutically acceptable forms thereof, wherein:

n_{XV} is an integer selected from 1 through 2;

A_{XV} and Q_{XV} are independently selected from the group consisting of $-CH_2(CR_{XV-37}R_{XV-38})_{vXV}-(CR_{XV-33}R_{XV-34})_{uXV}-T_{XV}-(CR_{XV-35}R_{XV-36})_{wXV}-H$,

AQ-1



and

alkylthioalkyl, alkyl, alkenyl, haloalkoxy, and haloalkoxyalkyl with the proviso that R_{XV-30} is selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

R_{XV-30}, when bonded to A_{XV-1}, is taken together to form an intra-ring linear spacer connecting the A_{XV-1}-carbon at the point of attachment of R_{XV-30} to the point of bonding of a group selected from the group consisting of R_{XV-10}, R_{XV-11}, R_{XV-12}, R_{XV-31}, and R_{XV-32} wherein said intra-ring linear spacer is selected from the group consisting of a covalent single bond and a spacer moiety having from 1 through 6 contiguous atoms to form a ring selected from the group consisting of a cycloalkyl having from 3 through 10 contiguous members, a cycloalkenyl having from 5 through 10 contiguous members, and a heterocyclyl having from 5 through 10 contiguous members;

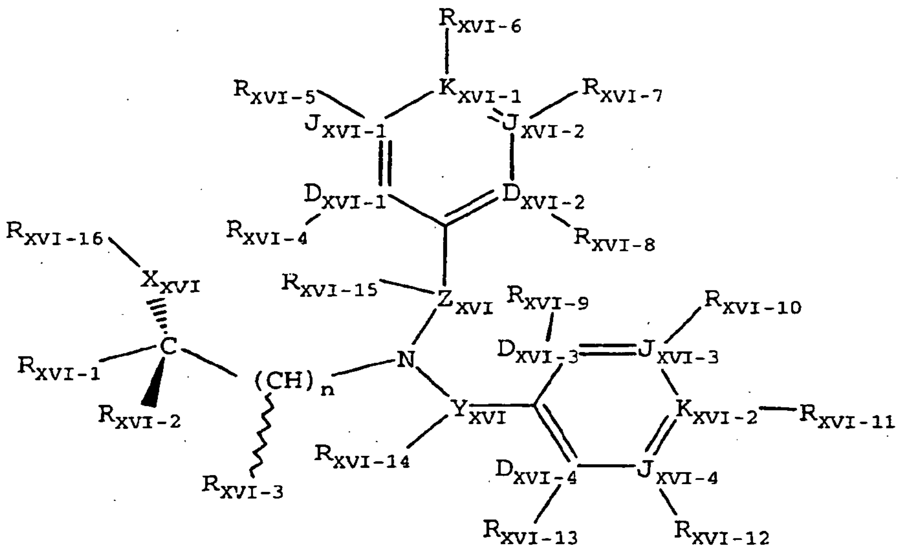
R_{XV-30}, when bonded to A_{XV-1}, is taken together to form an intra-ring branched spacer connecting the A_{XV-1}-carbon at the point of attachment of R_{XV-30} to the points of bonding of each member of any one of substituent pairs selected from the group consisting of subsitituent pairs R_{XV-10} and R_{XV-11}, R_{XV-10} and R_{XV-31}, R_{XV-10} and R_{XV-32}, R_{XV-10} and R_{XV-12}, R_{XV-11} and R_{XV-31}, R_{XV-11} and R_{XV-32}, R_{XV-11} and R_{XV-12}, R_{XV-31} and R_{XV-32}, R_{XV-31} and R_{XV-12}, and R_{XV-32} and R_{XV-12} and wherein said intra-ring branched spacer is selected to form two rings selected from the group consisting of cycloalkyl having from 3 through 10 contiguous members, cycloalkenyl having from 5 through 10 contiguous members, and heterocyclyl having from 5 through 10 contiguous members;

R_{XV-4}, R_{XV-5}, R_{XV-6}, R_{XV-7}, R_{XV-8}, R_{XV-9}, R_{XV-10}, R_{XV-11}, R_{XV-12}, R_{XV-13}, R_{XV-31}, R_{XV-32}, R_{XV-33}, R_{XV-34}, R_{XV-35}, and R_{XV-36} are independently selected from the group consisting of hydrido, carboxy, heteroaralkylthio, heteroaralkoxy, cycloalkylamino, acylalkyl, acylalkoxy, aroylalkoxy, heterocyclyloxy, aralkylaryl, aralkyl, aralkenyl, aralkynyl, heterocyclyl, perhaloaralkyl, aralkylsulfonyl, aralkylsulfonylalkyl, aralkylsulfinyl, aralkylsulfinylalkyl, halocycloalkyl, halocycloalkenyl, cycloalkylsulfinyl, cycloalkylsulfinylalkyl, cycloalkylsulfonyl, cycloalkylsulfonylalkyl, heteroarylamino, N-heteroarylamino-N-alkylamino, heteroarylaminoalkyl, haloalkylthio, alkanoyloxy, alkoxy, alkoxyalkyl, haloalkoxylalkyl, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, cycloalkoxyalkyl, cycloalkylalkoxy, cycloalkenyloxyalkyl, cycloalkylenedioxy, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxy, halocycloalkenyloxyalkyl, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, arylthioalkyl, heteroaralkoxyalkyl, alkylsulfinyl, alkylsulfinylalkyl, arylsulfinylalkyl, arylsulfonylalkyl, heteroarylsulfinylalkyl, heteroarylsulfonylalkyl, alkylsulfonyl, alkylsulfonylalkyl, haloalkylsulfinylalkyl, haloalkylsulfonylalkyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkylamidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, heterocyclylsulfonyl, heterocyclylthio, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkenyloxy, alkenyloxyalky, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkylalkanoyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkenyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, heteroaralkynyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkenyl, heteroarylalkenyl, carboxyalkyl, carboalkoxy, alkoxycarboxamido, alkylamidocarbonylamido, alkylamidocarbonylamido, carboalkoxyalkyl, carboalkoxyalkenyl, carboaralkoxy, carboxamido, carboxamidoalkyl, cyano, carbohaloalkoxy, phosphono, phosphonoalkyl, diaralkoxyphosphono, and diaralkoxyphosphonoalkyl with the provisos that R_{XV-4}, R_{XV-5}, R_{XV-6}, R_{XV-7}, R_{XV-8}, R_{XV-9}, R_{XV-10}, R_{XV-11}, R_{XV-12}, R_{XV-13}, R_{XV-31}, R_{XV-32}, R_{XV-33}, R_{XV-34}, R_{XV-35}, and R_{XV-36} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen, that no more than three of the R_{XV-33} and R_{XV-34} substituents are simultaneously selected from other than the group consisting of hydrido and halo, and that no more than three of the R_{XV-35} and R_{XV-36} substituents are simultaneously selected from other than the group consisting of hydrido and halo;

R_{XV-9}, R_{XV-10}, R_{XV-11}, R_{XV-12}, R_{XV-13}, R_{XV-31}, and R_{XV-32} are independently selected to be oxo with the provisos that B_{XV-1}, B_{XV-2}, D_{XV-3}, D_{XV-4}, J_{XV-3}, J_{XV-4}, and K_{XV-2} are independently selected from the group consisting of C and S, no more than two of R_{XV-9}, R_{XV-10}, R_{XV-11}, R_{XV-12}, R_{XV-13}, R_{XV-31}, and R_{XV-32} are simultaneously oxo, and that R_{XV-9}, R_{XV-10}, R_{XV-11}, R_{XV-12}, R_{XV-13}, R_{XV-31}, and R_{XV-32} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

R_{XV-4} and R_{XV-5}, R_{XV-5} and R_{XV-6}, R_{XV-6} and R_{XV-7}, R_{XV-7} and R_{XV-8}, R_{XV-9} and R_{XV-10}, R_{XV-10} and R_{XV-11}, R_{XV-11} and R_{XV-31}, R_{XV-31} and R_{XV-32}, R_{XV-32} and R_{XV-12}, and R_{XV-12} and R_{XV-13} are independently selected to form spacer pairs wherein a spacer pair is taken together to form a linear moiety having from 3 through 6 contiguous atoms connecting the points of bonding of said spacer pair members to form a ring selected from the group consisting of a cycloalkenyl ring having 5 through 8 contiguous members, a partially saturated heterocyclyl ring having 5 through 8 contiguous members, a heteroaryl ring having 5 through 6 contiguous members, and an aryl with the provisos that no more than one of the group consisting of spacer pairs R_{XV-4} and R_{XV-5}, R_{XV-5} and R_{XV-6}, R_{XV-6} and R_{XV-7}, R_{XV-7} and R_{XV-8} is used at the same time and that no more than one of the group consisting of spacer

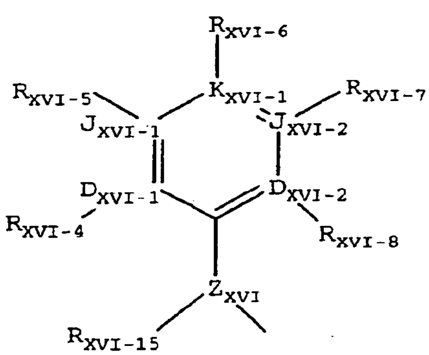
cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(2,3-dichlorophenoxy)phenyl][(3-pentafluoroethyl) cyclohexylmethyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(2,3-dichlorophenoxy)phenyl][(3-trifluoromethoxy) cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(2,3-dichlorophenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)cyclo-hexyl-methyl]amino]-1,1,1 -trifluoro-2-propanol;
3-[[3-(4-fluorophenoxy)phenyl](cyclohexylmethyl)amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(4-fluorophenoxy)phenyl](cyclopentylmethyl)amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(4-fluorophenoxy)phennyl](cyclopropylmethyl)amino]-1,1,1-triflouro-2-propanol;
3-[[3-(4-fluorophenoxy)phenyl][(3-trifluoromethyl) cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(4-fluorophenoxy)phenyl][(3-pentafluoroethyl) cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(4-fluorophenoxy)phenyl][(3-trifluoromethoxy) cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(4-fluorophenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-trifluoromethoxybenzyloxy]phenyl] (cyclohexylmethyl)amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-trifluoromethoxybenzyloxy)phenyl] (cyclopentylmethyl)amino]-1,1,1 -trifluoro-2-propanol;
3-[[3-(3-trifluoromethoxybenzyloxy)phenyl] (cyclopropylmethyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-trifluoromethoxybenzyloxy)phenyl][(3-trifluoromethyl)cyclohexyl-methyl]amino]-1,1,1 -trifluoro-2-propanol;
3-[[3-(3-trifluoromethoxybenzyloxy)phenyl][(3-pentafluoroethyl)cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-trifluoromethoxybenzyloxy]phenyl][(3-trifluoromethoxy)cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-trifluoromethoxybenzyloxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)-cyclohexylmethyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-trifluoromethylbenzyloxy)phenyl] (cyclohexylmethyl)amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-trifluoromethylbenzyloxy)phenyl] (cyclopentylmethyl)amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-trifluoromethylbenzyloxy)phenyl] (cyclopropylmethyl)amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-trifluoromethylbenzyloxy)phenyl][(3-trifluoromethyl)cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-trifluoromethylbenzyloxy)phenyl][(3-pentafluoroethyl)cyclohexyl-methyl]amino]-1,1,1 -trifluoro-2-propanol;
3-[[3-(3-trifluoromethylbenzyloxy)phenyl][(3-trifluoromethoxy)cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[3-(3-trifluoromethylbenzyloxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)cyclohexyl-methyl]amino]-1,1,1-trifluoro-2-propanol;
3-[[[(3-trifluoromethyl)phenyl]methyl](cyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
3-[[[(3-pentafluoroethyl)phenyl]methyl](cyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
3-[[[(3-trifluoromethoxy)phenyl]methyl](cyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl] methyl](cyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
3-[[[(3-trifluoromethyl)phenyl]methyl] (4-methylcyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
3-[[[(3-pentafluoroethyl)phenyl]methyl] (4-methylcyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
3-[[[(3-trifluoromethoxy)phenyl]methyl] (4-methylcyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl] (4-methylcyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
3-[[[(3-trifluoromethyl]phenyl]methyl](3-trifluoromethylcyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
3-[[[(3-pentafluoroethyl)phenyl]methyl](3-trifluoromethylcyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
3-[[[(3-trifluoromethoxy)phenyl]methyl](3-trifluoromethylcyclohexyl)amino]-1,1,1-trifluoro-2-propanol;
3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl](3-trifluoromethylcyclohexyl)amino]-1,1,1-trifluoro-2-propanol;



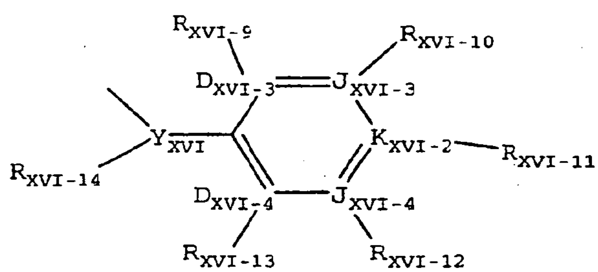
Formula XVI

and pharmaceutically acceptable forms thereof, wherein:

n_{XVI} is an integer selected from 1 through 4;
X_{XVI} is oxy;
R_{XVI-1} is selected from the group consisting of haloalkyl, haloalkenyl, haloalkoxymethyl, and haloalkenyloxymethyl with the proviso that R_{XVI-1} has a higher Cahn-Ingold-Prelog stereochemical system ranking than both R_{XVI-2} and $(CHR_{XVI-3})_n$-$N(A_{XVI})Q_{XVI}$ wherein A_{XVI} is Formula XVI-(II) and Q is Formula XVI-(III);



XVI-II



XVI-III

R_{XVI-16} is selected from the group consisting of hydrido, alkyl, acyl, aroyl, heteroaroyl, trialkylsilyl, and a spacer selected from the group consisting of a covalent single bond and a linear spacer moiety having a chain length of 1 to 4 atoms linked to the point of bonding of any aromatic substituent selected from the group consisting of R_{XVI-4}, R_{XVI-8}, R_{XVI-9}, and R_{XVI-13} to form a heterocyclyl ring having from 5 through 10 contiguous members;
D_{XVI-1}, D_{XVI-2}, J_{XVI-1}, J_{XVI-2} and K_{XVI-1} are independently selected from the group consisting of C, N, O, S and covalent bond with the provisos that no more than one of D_{XVI-1}, D_{XVI-2}, J_{XVI-1}, J_{XVI-2} and K_{XVI-1} is a covalent bond, no more than one D_{XVI-1}, D_{XVI-2}, J_{XVI-1}, J_{XVI-2} and K_{XVI-1} is be O, no more than one of D_{XVI-1}, D_{XVI-2}, J_{XVI-1}, J_{XVI-2} and K_{XVI-1} is S, one of D_{XVI-1}, D_{XVI-2}, J_{XVI-1}, J_{XVI-2} and K_{XVI-1} must be a covalent bond when two of D_{XVI-1}, D_{XVI-2},

R_{XVI-11} and R_{XVI-12}, and R_{XVI-12} and R_{XIV-13} are independently selected to form spacer pairs wherein a spacer pair is taken together to form a linear moiety having from 3 through 6 contiguous atoms connecting the points of bonding of said spacer pair members to form a ring selected from the group consisting of a cycloalkenyl ring having 5 through 8 contiguous members, a partially saturated heterocyclyl ring having 5 through 8 contiguous members, a heteroaryl ring having 5 through 6 contiguous members, and an aryl with the provisos that no more than one of the group consisting of spacer pairs R_{XVI-4} and R_{XVI-5}, R_{XVI-5} and R_{XVI-6}, R_{XVI-6} and R_{XVI-7}, and R_{XVI-7} and R_{XVI-8} is used at the same time and that no more than one of the group consisting of spacer pairs R_{XIV-9} and R_{XVI-10}, R_{XVI-10} and R_{XVI-11}, R_{XVI-11} and R_{XVI-12}, and R_{XVI-12} and R_{XVI-13} can be used at the same time;

R_{XVI-4} and R_{XVI-9}, R_{XVI-4} and R_{XVI-13}, R_{XVI-8} and R_{XVI-9}, and R_{XVI-8} and R_{XVI-13} is independently selected to form a spacer pair wherein said spacer pair is taken together to form a linear moiety wherein said linear moiety forms a ring selected from the group consisting of a partially saturated heterocyclyl ring having from 5 through 8 contiguous members and a heteroaryl ring having from 5 through 6 contiguous members with the proviso that no more than one of the group consisting of spacer pairs R_{XVI-4} and R_{XVI-9}, R_{XVI-4} and R_{XVI-13}, R_{XVI-8} and R_{XVI-9}, and R_{XVI-8} and R_{XVI-13} is used at the same time.

[0130] Compounds of Formula XVI and their methods of manufacture are disclosed in PCT Publication No. WO 00/18724, which is incorporated herein by reference in its entirety for all purposes.

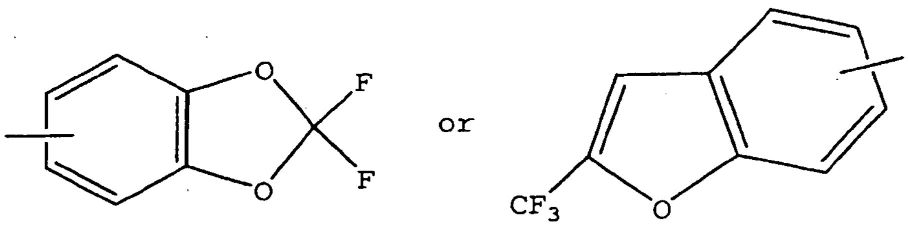
[0131] In a preferred embodiment, the CETP inhibitor is selected from the following compounds of Formula XVI:

(2R)-3-[[3-(3-trifluoromethoxyphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1 -trifluoro-2-propanol;
(2R)-3-[[3-(3-isopropylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
(2 R)-3-[[3-(3-cyclopropylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1 -trifluoro-2-propanol;
(2R)-3-[[3-(3-(2-furyl)phenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(2,3-dichlorophenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(4-fluorophenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(4-methylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(2-fluoro-5-bromophenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(4-chloro-3-ethylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl][[3-(1,1,2,2-tetrafluoro-ethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-[3-(pentafluoroethyl)phenoxy]phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(3,5-dimethylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(3-ethylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(3-t-butylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol:
(2R)-3-[[3-(3-methylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1 -trifluoro-2-propanol;
(2R)-3-[[3-(5,6,7,8-tetrahydro-2-naphthoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(phenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-[3-(N,N-dimethylamino)phenoxy]phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[[3-(1,1,2,2,-tetrafluoroethoxy)phenyl]methyl][3-[[3-(trifluoromethoxy)-phenyl]methoxy]phenyl]amino]-1,1,1 -trifluoro-2-propanol;
(2R)-3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3-[[3-(trifluoro-methyl)phenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;

(2R)-3-[[[3-(pentafluoroethyl)phenyl]methyl][3-[cyclohexylmethoxy]phenyl]-amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(2-difluoromethoxy-4-pyridyloxy)phenyl][[3-(pentafluoroethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(2-trifluoromethyl-4-pyridyloxy)phenyl][[3-(pentafluoroethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(3-difluoromethoxyphenoxy)phenyl][[3-(pentafluoroethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[[3-(3-trifluoromethylthio)phenoxy]phenyl][[3-(pentafluoroethyl)phenyl]-methyl]amino]-1,1,1 -trifluoro-2-propanol;
(2R)-3-[[3-(4-chloro-3-trifluoromethylphenoxy)phenyl][[3-(pentafluoroethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(3-trifluoromethoxyphenoxy)phenyl][[3-(heptafluoropropyl)phenyl]-methyl]amino]-1,1,1 -trifluoro-2-propanol;
(2R)-3-[[3-(3-isopropylphenoxy)phenyl][[3-(heptafluoropropyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(3-cyclopropylphenoxy)phenyl][[3-(heptafluoropropyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(3-(2-furyl)phenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(2,3-dichlorophenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(4-fluorophenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(4-methylphenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]amino]-1,1,1,-trifluoro-2-propanol;
(2R)-3-[[3-(2-fluoro-5-bromophenoxy)phenyl][[3-(heptafluoropropyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(4-chloro-3-ethylphenoxy)phenyl][[3-(heptafluoropropyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl][[3-(heptafluoropropyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-[3-(pentafluoroethyl)phenoxy]phenyl][[3-(heptafluoropropyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(3,5-dimethylphenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(3-ethylphenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(3-t-butylphenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(3-methylphenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(5,6,7,8-tetrahydro-2-naphthoxy)phenyl][[3-(heptafluoropropyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(phenoxy)phenyl][[3-(heptafluoropropyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-[3-(N,N-dimethylamino)phenoxy]phenyl][[3-(heptafluoropropyl)phenyl]-methyl]amino]-1,1,1 -trifluoro-2-propanol;
(2R)-3-[[[3-(heptafluoropropyl)phenyl]methyl][3-[[3-(trifluoromethoxy)phenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[[3-(heptafluoropropyl)phenyl]methyl][3-[[3-(trifluoromethyl)phenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[[3-(heptafluoropropyl)phenyl]methyl][3-[[3,5-dimethylphenyl]methoxy]-phenyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[[3-(heptafluoropropyl)phenyl]methyl][3-[[3-(trifluoromethylthio)phenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[[3-(heptafluoropropyl)phenyl]methyl][3-[[3,5-difluorophenyl]methoxy]-phenyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[[3-(heptafluoropropyl)phenyl]methyl][3-[cyclohexylmethoxy]phenyl]-amino]-1,1,1 -trifluoro-2-propanol;
(2R)-3-[[3-(2-difluoromethoxy-4-pyridyloxy)phenyl][[3-(heptafluoropropyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(2-trifluoromethyl-4-pyridyloxy)phenyl][[3-(heptafluoropropyl)phenyl]-methyl]amino]-1,1,1 -trifluoro-2-propanol;

(2R)-3-[[[3-(3-trifluoromethylthio)phenoxy]phenyl][[2-fluoro-5-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(4-chloro-3-trifluoromethylphenoxy)phenyl)[[2-fluoro-5-(trifluoro-methyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(3-trifluoromethoxyphenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(3-isopropylphenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)phenyl]-methyl]amino]l-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(3-cyclopropylphenoxy)phenyl][[2-flouro-4-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(3-(2-furyl)phenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(2,3-dichlorophenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(4-fluorophenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(4-methylphenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(2-fluoro-5-bromophenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(4-chloro-3-ethylphenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl]
[[2-fluoro-4-(trifluoromethyl)phenyl]methyl]amino]-1,1,1 -trifluoro-2-propanol;
(2R)-3-[[3-[3-(pentafluoroethyl)phenoxy]phenyl][[2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(3,5-dimethylphenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)phenyl]-methyl]aminol-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(3-ethylphenoxy)phenyl][[2-fluoro-4- (trifluoromethyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(3-t-butylphenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(3-methylphenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(5,6,7,8-tetrahydro-2-naphthoxy)phenyl][[2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(phenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)
phenyl]methyl]amino]-1,1,1 -trifluoro-2-propanol;
(2R)-3-[[3-[3-(N,N-dimethylamino)phenoxy]phenyl][[2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[[2-fluoro-4-(trifluoromethyl)phenyl]methyl][3-[[3-(trifluoromethoxy)phenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
(3R)-3-[[[2-fluoro-4-(trifluoromethyl)phenyl]methyl][3-[[3-(trifluoromethyl)phenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[[2-fluoro-4-(trifluoromethyl)phenyl]methyl][3-[[3,5-dimethylphenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[[2-fluoro-4-(trifluoromethyl)phenyl]methyl][3-[[3-(trifluoromethylthio)-phenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[[2-fluoro-4-(trifluoromethyl)phenyl]methyl][3-[[3,5-difluorophenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[[2-fluoro-4-(trifluoromethyl)phenyl]methyl][3-[cyclohexylmethoxy]-phenyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(2-difluoromethoxy-4-pyridyloxy)phenyl][[2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(2-trifluoromethyl-4-pyridyloxy)phenyl][[2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[3-(3-difluoromethoxyphenoxy)phenyl][[2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
(2R)-3-[[[3-(3-trifluoromethylthio)phenoxy]phenyl][[2-fluoro-4-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol; and

R_{XVII-6} and/or R_{XVII-7} denote a radical according to the formula



R_{XVII-8} denotes a hydrogen or halogen, and

R_{XVII-9} denotes a hydrogen, halogen, azido, trifluoromethyl, hydroxyl, trifluoromethoxy, a straight-chain or branched alkoxy or alkyl containing up to 6 carbon atoms each, or a radical according to the formula $NR_{XVII-16}R_{XVII-17}$;

$R_{XVII-16}$ and $R_{XVII-17}$ are identical or different and have the meaning of R_{XVII-4} and R_{XVII-5} above; or

R_{XVII-8} and R_{XVII-9} together form a radical according to the formula =O or $=NR_{XVII-18}$;

$R_{XVII-18}$ denotes a hydrogen or a straight-chain or branched alkyl, alkoxy or acyl containing up to 6 carbon atoms each;

L_{XVII} denotes a straight-chain or branched alkylene or alkenylene chain containing up to 8 carbon atoms each, which are optionally substituted with up to two hydroxyl groups;

T_{XVII} and X_{XVII} are identical or different and denote a straight-chain or branched alkylene chain containing up to 8 carbon atoms; or

T_{XVII} and X_{XVII} denotes a bond;

V_{XVII} denotes an oxygen or sulfur atom or $-NR_{XVII-19}$;

$R_{XVII-19}$ denotes a hydrogen or a straight-chain or branched alkyl containing up to 6 carbon atoms or a phenyl;

E_{XVII} denotes a cycloalkyl containing 3 to 8 carbon atoms, or a straight-chain or branched alkyl containing up to 8 carbon atoms, which is optionally substituted with a cycloalkyl containing 3 to 8 carbon atoms or a hydroxyl, or a phenyl, which is optionally substituted with a halogen or trifluoromethyl;

R_{XVII-1} and R_{XVII-2} are identical or different and denote a cycloalkyl containing 3 to 8 carbon atoms, hydrogen, nitro, halogen, trifluoromethyl, trifluoromethoxy, carboxy, hydroxy, cyano, a straight-chain or branched acyl, alkoxycarbonyl or alkoxy with up to 6 carbon atoms, or $NR_{XVII-20}R_{XVII-21}$;

$R_{XVII-20}$ and $R_{XVII-21}$ are identical or different and denote hydrogen, phenyl, or a straight-chain or branched alkyl with up to 6 carbon atoms; and or

R_{XVII-1} and/or R_{XVII-2} are straight-chain or branched alkyl with up to 6 carbon atoms, optionally substituted with halogen, trifluoromethoxy, hydroxy, or a straight-chain or branched alkoxy with up to 4 carbon atoms, aryl containing 6-10 carbon atoms optionally substituted with up to five of the same or different substituents selected from halogen, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, nitro, straight-chain or branched alkyl, acyl, hydroxyalkyl, alkoxy with up to 7 carbon atoms and $NR_{XVII-22}R_{XVII-23}$;

$R_{XVII-22}$ and $R_{XVII-23}$ are identical or different and denote hydrogen, phenyl or a straight-chain or branched akyl up to 6 carbon atoms; and/or

R_{XVII-1} and R_{XVII-2} taken together form a straight-chain or branched alkene or alkane with up to 6 carbon atoms optionally substituted with halogen, trifluoromethyl, hydroxy or straight-chain or branched alkoxy with up to 5 carbon atoms;

R_{XVII-3} denotes hydrogen, a straight-chain or branched acyl with up to 20 carbon atoms, a benzoyl optionally substituted with halogen, trifluoromethyl, nitro or trifluoromethoxy, a straight-chained or branched fluoroacyl with up to 8 carbon atoms and 7 fluoro atoms, a cycloalkyl with 3 to 7 carbon atoms, a straight chained or branched alkyl with up to 8 carbon atoms optionally substituted with hydroxyl, a straight-chained or branched alkoxy with up to 6 carbon atoms optionally substituted with phenyl which may in turn be substituted with halogen, nitro, trifluoromethyl, trifluoromethoxy, or phenyl or a tetrazol substitued phenyl, and/or an alkyl that is optionally substituted with a group according to the formula $-OR_{XVII-24}$;

$R_{XVII-24}$ is a straight-chained or branched acyl with up to 4 carbon atoms or benzyl.

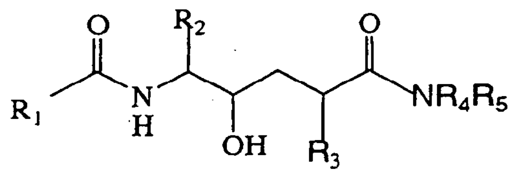
[0133] Compounds of Formula XVII and their methods of manufacture are disclosed in PCT Publication No. WO 98/39299, which is incorporated herein by reference in its entirety for all purposes.

[0134] Another class of CETP inhibitors that finds utility with the present invention consists of 4-Phenyltetrahydroquinolines of Formula XVIII

from a unit surface area, therefore, the intrinsic dissolution rate is referred to in units of $mg/min.cm^2$.

[0138] The compositions and methods of the invention are particularly useful for compounds with an intrinsic dissolution rate of preferably less than 0.1 $mg/min.cm^2$ and more preferably with less than 0.05 $mg/min.cm^2$.

[0139] Turning now to the chemical structures of specific CCR1 inhibitors, one class of CCR1 inhibitors that finds utility with the present invention consists of dihydroxyhexanoic acid derivatives having the Formula CCR1-I



CCR1-I

wherein R_1 is (C_2-C_9) heteroaryl optionally substituted with one, two or three substituents independently selected from the group consisting of hydrogen, halo, cyano, (C_1-C_6)alkyl optionally substituted with one, two or three fluorine atoms, hydroxy, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, HO-(C=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-O-(C=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-(C=O)-O-, (C_1-C_6)alkyl-(C=O)-O-(C_1-C_6) alkyl, H(O=C)-, H(O=C)-(C_1-C_6)alkyl, (C_1-C_6)alkyl(O=C)-, (C_1-C_6)alkyl(O=C)-(C_1-C_6)alkyl, NO_2, amino, (C_1-C_6) alkylamino, [(C_1-C_6)alkyl]$_2$amino, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, [(C_1-C_6)alkyl]$_2$amino(C_1-C_6)alkyl, H_2N-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6) alkyl]$_2$N-(C=O)-, H_2N(C=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-HN(C=O)-(C_1-C_6)alkyl, [(C_1-C_6)alkyl]$_2$N-(C=O)-(C_1-C_6)alkyl, H (O=C)-NH-, (C_1-C_6)alkyl(C=O)-NH, (C_1-C_6)alkyl(C=O)-[NH](C_1-C_6)alkyl, (C_1-C_6)alkyl(C=O)-[N(C_1-C_6)alkyl](C_1-C_6) alkyl, (C_1-C_6)alkyl-S-, (C_1-C_6)alkyl-(S=O)-, (C_1-C_6)alkyl-SO_2-, (C_1-C_6)alkyl-SO_2-NH-, H_2N-SO_2-, H_2N-SO_2-(C_1-C_6) alkyl, (C_1-C_6)alkylHN-SO_2-(C_1-C_6)alkyl, [(C_1-C_6)alkyl]$_2$N-SO_2-(C_1-C_6)alkyl, CF_3SO_3-, (C_1-C_6)alkyl-SO_3-, phenyl, (C_3-C_{10})cycloalkyl, (C_2-C_9)heterocycloalkyl, and (C_2-C_9)heteroaryl;

wherein R_2 is phenyl-(CH_2)$_m$-, naphthyl-(CH_2)$_m$-, (C_3-C_{10})cycloalkyl-(CH_2)$_m$-, (C_1-C_6)alkyl or (C_2-C_9)heteroaryl-(CH_2)$_m$-, wherein each of said phenyl, naphthyl, (C_3-C_{10})cycloalkyl or (C_2-C_9)heteroaryl moieties of said phenyl-(CH_2)$_m$-, naphthyl-(CH_2)$_m$-, (C_3-C_{10})cycloalkyl-(CH_2)$_m$- or (C_2-C_9)heteroaryl-(CH_2)$_m$- groups may optionally be substituted with one, two, or three substituents independently selected from the group consisting of hydrogen, halo, cyano, (C_1-C_6)alkyl, hydroxy, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, HO-(C=O)-, (C_1-C_6) alkyl-O-(C=O)-, HO-(C=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-O-(C=O)-(C_1-C_6)alkyl,(C_1-C_6)alkyl-(C=O)-O-, (C_1-C_6) alkyl-(C=O)-O-(C_1-C_6)alkyl, H(O=C)-, H(O=C)-(C_1-C_6)alkyl, (C_1-C_6)alkyl(O=C)-, (C_1-C_6)alkyl(O=C)-(C_1-C_6)alkyl, NO_2, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$amino, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, [(C_1-C_6)alkyl]$_2$amino(C_1-C_6)alkyl, H_2N-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$N-(C=O)-, H_2N(C=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-HN(C=O)-(C_1-C_6)alkyl, [(C_1-C_6)alkyl]$_2$N-(C=O)-(C_1-C_6) alkyl, H(O=C)-NH-, (C_1-C_6)alkyl(C=O)-NH, (C_1-C_6)alkyl(C=O)-[NH](C_1-C_6)alkyl, (C_1-C_6)alkyl(C=O)-[N(C_1-C_6)alkyl](C_1-C_6)alkyl, (C_1-C_6)alkyl-S-, (C_1-C_6) alkyl-(S=O)-, (C_1-C_6)alkyl-SO_2-, (C_1-C_6)alkyl-SO2-NH-, H_2N-SO_2-, H_2N-SO_2-(C_1-C_6)alkyl, (C_1-C_6)alkyl-HN-SO_2-(C_1-C_6)alkyl, [(C_1-C_6)alkyl]$_2$N-SO_2-(C_1-C_6)alkyl, CF_3SO_3-, (C_1-C_6)alkyl-SO_3-, phenyl, phenoxy, benzyloxy, (C_3-C_{10})cycloalkyl, (C_2-C_9)heterocycloalkyl, and (C_2-C_9)heteroaryl;

wherein R^3 is hydrogen, (C_1-C_{10})alkyl, (C_3-C_{10})cycloalkyl-(CH_2)$_n$-, (C_2-C_9)heterocycloalkyl-(CH_2)$_n$-, (C_2-C_9)heteroaryl-(CH_2)$_n$- or aryl-(CH_2)$_n$-; wherein n is an interger from zero to six;

wherein said R_3 (C_1-C_{10})alkyl group may optionally be substituted with one or more substituents, (preferably from one to three substituents) independently selected from hydrogen, halo, CN, (C_1-C_6)alkyl, hydroxy, hydroxy-(C_1-C_6) alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, HO-(C=O)-(C_1-C_6)alkyl, (C_1-C_6) alkyl-O-(C=O)-(C_1-C_6)alkyl,(C_1-C_6)alkyl-(C=O)-O-, (C_1-C_6)alkyl-(C=O)-O-(C_1-C_6)alkyl, H(O=C)-, H(O=C)-(C_1-C_6) alkyl, (C_1-C_6)alkyl(O=C)-, (C_1-C_6)alkyl(O=C)-(C_1-C_6)alkyl, NO_2, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$amino, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, [(C_1-C_6)alkyl]$_2$amino(C_1-C_6)alkyl, H_2N-(C=O)-, (C_1-C_6) alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$N-(C=O)-, H_2N(C=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-HN(C=O)-(C_1-C_6)alkyl, [(C_1-C_6) alkyl]$_2$N-(C=O)-(C_1-C_6)alkyl, H(O=C)-NH-, (C_1-C_6)alkyl(C=O)-NH, (C_1-C_6)alkyl(C=O)-[NH](C_1-C_6)alkyl, (C_1-C_6)alkyl (C=O)-[N(C_1-C_6)alkyl](C_1-C_6)alkyl, (C_1-C_6)alkyl-S-, (C_1-C_6)alkyl-(S=O)-, (C_1-C_6)alkyl-SO_2-, (C_1-C_6)alkyl-SO_2-NH-, H_2N-SO_2-, H_2N-SO_2-(C_1-C_6)alkyl, (C_1-C_6)alkylHN-SO_2-(C_1-C_6)alkyl, [(C_1-C_6)alkyl]$_2$ N-SO_2-(C_1-C_6)alkyl, CF_3SO_3-, (C_1-C_6)alkyl-SO_3-, phenyl, (C_3-C_{10})cycloalkyl, (C_2-C_9)heterocycloalkyl, and (C_2-C_9)heteroaryl; and wherein any of the

$(C_1\text{-}C_6)$alkyl, HO-(C=O)-, $(C_1\text{-}C_6)$alkyl-O-(C=O)-, HO-(C=O)-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-O-(C=O)-$(C_1\text{-}C_6)$alkyl,$(C_1\text{-}C_6)$alkyl-(C=O)-O-, $(C_1\text{-}C_6)$alkyl-(C=O)-O-$(C_1\text{-}C_6)$alkyl, H(O=C)-, H(O=C)-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl(O=C)-, $(C_1\text{-}C_6)$alkyl(O=C)-$(C_1\text{-}C_6)$alkyl, NO_2, amino, $(C_1\text{-}C_6)$alkylamino, $[(C_1\text{-}C_6)alkyl]_2$amino, amino$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylamino$(C_1\text{-}C_6)$alkyl, $[(C_1\text{-}C_6)alkyl]_2$amino$(C_1\text{-}C_6)$alkyl, H_2N-(C=O)-, $(C_1\text{-}C_6)$alkyl-NH-(C=O)-, $[(C_1\text{-}C_6)alkyl]_2N$-(C=O)-, H_2N(C=O)-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-HN(C=O)-$(C_1\text{-}C_6)$alkyl, $[(C_1\text{-}C_6)alkyl]_2N$-(C=O)-$(C_1\text{-}C_6)$alkyl, H(O=C)-NH-, $(C_1\text{-}C_6)$alkyl(C=O)-NH, $(C_1\text{-}C_6)$alkyl(C=O)-[NH]$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl(C=O)-[N$(C_1\text{-}C_6)$alkyl]$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-S-, $(C_1\text{-}C_6)$alkyl-(S=O)-, $(C_1\text{-}C_6)$alkyl-SO_2-, $(C_1\text{-}C_6)$alkyl-SO_2-NH-, H_2N-SO_2-, H_2N-SO_2-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-HN-SO_2-$(C_1\text{-}C_6)$alkyl, $[(C_1\text{-}C_6)alkyl]_2N$-$SO_2$-$(C_1\text{-}C_6)$alkyl, CF_3SO_3-, $(C_1\text{-}C_6)$alkyl- SO_3-, phenyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_2\text{-}C_9)$heterocycloalkyl, and $(C_2\text{-}C_9)$heteroaryl; wherein one of the carbon-carbon bonds of said five to seven membered carbocyclic ring may optionally be fused to an optionally substituted phenyl ring, wherein said substitutents may be independently selected from hydrogen, halo, CN, $(C_1\text{-}C_6)$alkyl, hydroxy, hydroxy-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, HO-(C=O)-, $(C_1\text{-}C_6)$alkyl-O-(C=O)-, HO-(C=O)-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-O-(C=O)-$(C_1\text{-}C_6)$alkyl,$(C_1\text{-}C_6)$alkyl-(C=O)-O-, $(C_1\text{-}C_6)$alkyl-(C=O)-O-$(C_1\text{-}C_6)$alkyl, H(O=C)-, H(O=C)-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl(O=C)-, $(C_1\text{-}C_6)$alkyl(O=C)-$(C_1\text{-}C_6)$alkyl, NO_2, amino, $(C_1\text{-}C_6)$alkylamino, $[(C_1\text{-}C_6)alkyl]_2$amino, amino$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylamino$(C_1\text{-}C_6)$alkyl, $[(C_1\text{-}C_6)alkyl]_2$amino$(C_1\text{-}C_6)$alkyl, H_2N-(C=O)-, $(C_1\text{-}C_6)$alkyl-NH-(C=O)-, $[(C_1\text{-}C_6)alkyl]_2N$-(C=O)-, H_2N(C=O)-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-HN(C=O)-$(C_1\text{-}C_6)$alkyl, $[(C_1\text{-}C_6)alkyl]_2N$-(C=O)-$(C_1\text{-}C_6)$alkyl, H(O=C)-NH-, $(C_1\text{-}C_6)$alkyl(C=O)-NH, $(C_1\text{-}C_6)$alkyl(C=O)-[NH]$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl(C=O)-[N$(C_1\text{-}C_6)$alkyl]$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-S-, $(C_1\text{-}C_6)$alkyl-(S=O)-, $(C_1\text{-}C_6)$alkyl-SO_2-, $(C_1\text{-}C_6)$alkyl-SO_2-NH-, H_2N-SO_2-, H_2N-SO_2-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylHN-SO_2-$(C_1\text{-}C_6)$alkyl, $[(C_1\text{-}C_6)alkyl]_2N$-$SO_2$-$(C_1\text{-}C_6)$alkyl, CF_3SO_3-, $(C_1\text{-}C_6)$alkyl- SO_3-, phenyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_2\text{-}C_9)$heterocycloalkyl, and $(C_2\text{-}C_9)$heteroaryl;

wherein R_4 is hydrogen, $(C_1\text{-}C_6)$alkyl, hydroxy, $(C_1\text{-}C_6)$alkoxy, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy(C=O)-, $(C_3\text{-}C_{10})$cycloalkyl-$(CH_2)_q$-, $(C_2\text{-}C_9)$heterocycloalkyl-$(CH_2)_q$-, $(C_2\text{-}C_9)$heteroaryl-$(CH_2)_q$-, phenyl-$(CH_2)_q$-, or naphthyl-$(CH_2)_q$-; wherein said $(C_2\text{-}C_9)$heterocycloalkyl, $(C_2\text{-}C_9)$heteroaryl, phenyl and naphthyl groups may be optionally substituted with one or two substituents from the group consisting of hydrogen, halo, cyano, $(C_1\text{-}C_6)$alkyl, hydroxy, hydroxy-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, HO-(C=O)-, $(C_1\text{-}C_6)$alkyl-O-(C=O)-, HO-(C=O)-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-O-(C=O)-$(C_1\text{-}C_6)$alkyl,$(C_1\text{-}C_6)$alkyl-(C=O)-O-, $(C_1\text{-}C_6)$alkyl-(C=O)-O-$(C_1\text{-}C_6)$alkyl, H(O=C)-, H(O=C)-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$ alkyl(O=C)-, $(C_1\text{-}C_6)$alkyl(O=C)-$(C_1\text{-}C_6)$alkyl, NO_2, amino, $(C_1\text{-}C_6)$alkylamino, $[(C_1\text{-}C_6)alkyl]_2$amino, amino$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylamino $(C_1\text{-}C_6)$alkyl, $[(C_1\text{-}C_6)alkyl]_2$amino$(C_1\text{-}C_6)$alkyl, H_2N-(C=O)-, $(C_1\text{-}C_6)$alkyl-NH-(C=O)-, $[(C_1\text{-}C_6)alkyl]_2N$-(C=O)-, H_2N(C=O)-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-HN(C=O)-$(C_1\text{-}C_6)$alkyl, $[(C_1\text{-}C_6)alkyl]_2N$-(C=O)-$(C_1\text{-}C_6)$alkyl, H(O=C)-NH-, $(C_1\text{-}C_6)$alkyl(C=O)-NH, $(C_1\text{-}C_6)$alkyl(C=O)-[NH]$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl(C=O)-[N$(C_1\text{-}C_6)$alkyl]$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-S-, $(C_1\text{-}C_6)$alkyl-(S=O)-, $(C_1\text{-}C_6)$alkyl-SO_2-, $(C_1\text{-}C_6)$alkyl-SO_2-NH-, H_2N-SO_2-, H_2N-SO_2-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylHN-SO_2-$(C_1\text{-}C_6)$alkyl, $[(C_1\text{-}C_6)alkyl]_2N$-$SO_2$-$(C_1\text{-}C_6)$alkyl, CF_3SO_3-, $(C_1\text{-}C_6)$alkyl-SO_3, phenyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_2\text{-}C_9)$heterocycloalkyl, and $(C_2\text{-}C_9)$heteroaryl;

wherein R_5 is hydrogen, $(C_1\text{-}C_6)$alkyl or amino; or

R_4 and R_5 together with the nitrogen atom to which they are attached form a $(C_2\text{-}C_9)$heterocycloalkyl group optionally substituted with one or two substituents selected from the group consisting of hydrogen, halo, cyano, $(C_1\text{-}C_6)$alkyl, hydroxy, hydroxy-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, HO-(C=O)-, $(C_1\text{-}C_6)$alkyl-O-(C=O)-, HO-(C=O)-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-O-(C=O)-$(C_1\text{-}C_6)$alkyl,$(C_1\text{-}C_6)$alkyl-(C=O)-O-, $(C_1\text{-}C_6)$alkyl-(C=O)-O-$(C_1\text{-}C_6)$alkyl, H(O=C)-, H(O=C)-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$ alkyl(O=C)-, $(C_1\text{-}C_6)$alkyl(O=C)-$(C_1\text{-}C_6)$alkyl, NO_2, amino, $(C_1\text{-}C_6)$alkylamino, $[(C_1\text{-}C_6)alkyl]_2$ amino, amino$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylamino $(C_1\text{-}C_6)$alkyl, $[(C_1\text{-}C_6)alkyl]_2$amino$(C_1\text{-}C_6)$alkyl, H_2N-(C=O)-, $(C_1\text{-}C_6)$alkyl-NH-(C=O)-, $[(C_1\text{-}C_6)alkyl]_2N$-(C=O)-, H_2N(C=O)-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-HN(C=O)-$(C_1\text{-}C_6)$alkyl, $[(C_1\text{-}C_6)alkyl]_2N$-(C=O)-$(C_1\text{-}C_6)$alkyl, H(O=C)-NH-, $(C_1\text{-}C_6)$alkyl(C=O)-NH, $(C_1\text{-}C_6)$alkyl(C=O)-[NH]$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl(C=O)-[N$(C_1\text{-}C_6)$alkyl]$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-S-, $(C_1\text{-}C_6)$alkyl-(S=O)-, $(C_1\text{-}C_6)$alkyl-SO_2-, $(C_1\text{-}C_6)$alkyl-SO_2-NH-, H_2N-SO_2-, H_2N-SO_2-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylHN-SO_2-$(C_1\text{-}C_6)$alkyl, $[(C_1\text{-}C_6)alkyl]_2N$-$SO_2$-$(C_1\text{-}C_6)$alkyl, CF_3SO_3-, $(C_1\text{-}C_6)$alkyl-SO_3-, phenyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_2\text{-}C_9)$heterocycloalkyl, and $(C_2\text{-}C_9)$heteroaryl;

wherein R^6 is hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy-$(CH_2)_g$-, $(C_1\text{-}C_6)$alkoxy(C=O)-$(CH_2)_g$-, $(C_1\text{-}C_6)$alkyl-(SO_2)-$(CH_2)_g$-, $(C_6\text{-}C_{10})$aryloxy-$(CH_2)_g$-, $(C_6\text{-}C_{10})$aryloxy(C=O)-$(CH_2)_g$-, or $(C_6\text{-}C_{10})$aryl-(SO_2)-$(CH_2)_g$-;

wherein g is an integer from zero to four;

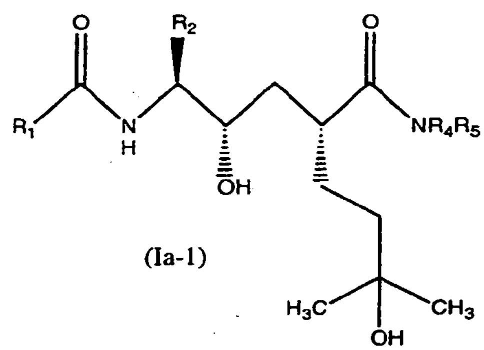
wherein m is an integer from zero to four;

wherein n is an interger from zero to six;

with the proviso that when one of R^4 or R^5 is hydrogen, and the other of R^4 or R^5 is $(C_1\text{-}C_6)$alkyl; R^2 is $(C_3\text{-}C_{10})$cycloalkyl or isopropyl and R^3 is $(C_3\text{-}C_5)$alkyl, phenyl, methylvinyl, dimethylvinyl, halovinyl, hydroxy$(C_1\text{-}C_3)$alkyl or amino$(C_1\text{-}C_4)$alkyl then R^1 must be other than indol-5-yl, 6-azaindol-2-yl, 2,3-dichloro-pyrrol-5-yl, 4-hydroxyquinolin-3-yl, 2-hydroxyquinoxalin-3-yl, 6-azaindolin-3-yl, or optionally substituted indol-2 or 3-yl;

quinoxaline-2-carboxylic acid 1 (S)-cyclohexylmethyl-2(S)-hydroxy-7-methyl-4(R)-methylcarbamoyl-octyl)-amide;
quinoxaline-2-carboxylic acid [1 (S)-benzyl-2(S)-hydroxy-4(S)-hydroxycarbamoyl-4-(1-hydroxy-4-methyl-cyclohexyl)-butyl]-amide;
quinoxaline-2-carboxylic acid [1(S)-benzyl-4(S)-(4,4-difluoro-1-hydroxy-cyclohexyl)-2(S)-hydroxy-4-hydroxycarbamoyl-but yl]-amide;
quinoxaline-2-carboxylic acid [1(S)-benzyl-4(S)-carbamoyl-4(S)-(4,4-difluoro-cyclohexyl)-2(S)-hydroxy-butyl]-amide;
quinoline-3-carboxylic acid (1 (S)-benzyl-4(S)-carbamoyl-4-cyclohexyl-2(S)-hydroxy-butyl)-amide;
quinoxaline-2-carboxylic acid (4(R)-carbamoyl-2(S)-hydroxy-7-methyl-1 (S)-thiophen-2-ylmethyl-octyl)-amide;
quinoxaline-2-carboxylic acid 1 (S)-benzyl-4(R)-carbamoyl-7-chloro-2(S)-hydroxy-oct-6-enyl)-amide;
quinoxaline-2-carboxylic acid 1 (S)-benzyl-4(R)-carbamoyl-2(S)-hydroxy-5-phenyl-pentyl)-amide;
N-1(S)-benzyl-4(R)-carbamoyl-7-fluoro-2(S)-hydroxy-7-methyl-octyl)-5,6-dichloro-nicotinamide;
quinoxaline-2-carboxylic acid (4(R)-carbamoyl-2(S)-hydroxy-7-methyl-1 (S)-thiazol-4(R)-ylmethyl-octyl)-amide;
benzothiazole-2-carboxylic acid 1 (S)-benzyl-4(R)-carbamoyl-7-fluoro-2(S)-hydroxy-7-methyl-octyl)-amide; and
benzofuran-2-carboxylic acid 1 (S)-benzyl-4(R)-carbamoyl-7-fluoro-2(S)-hydroxy-7-methyl-octyl)-amide.

[0149] In another preferred embodiment, the CCR1 compound has a formula Ia-1:



(Ia-1)

wherein the substituents are as defined above.

[0150] In a preferred method of making the compound Ia-1, the reaction is started with Scheme 1. In the herein described processes, the substituents are as defined for COR1-I, and the following:

R_7 is hydroxy, $(C_1\text{-}C_6)$alkyl, or phenyl wherein the phenyl group unsubstituted or substituted with one, two, or three $(C_1\text{-}C_6)$alkyl, hydroxy, or halogen groups;
R_8 is hydroxy or halogen;
R_9 is phenyl, naphthyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_1\text{-}C_6)$alkyl or $(C_2\text{-}C_9)$heteroaryl,

wherein each of said phenyl, naphthyl, $(C_3\text{-}C_{10})$cycloalkyl or $(C_2\text{-}C_9)$heteroaryl groups may be unsubstituted or substituted with one, two, or three substituents independently selected from the group consisting of halogen, cyano, and $(C_1\text{-}C_6)$alkyl;

P is a protecting group;
X is hydroxy or halogen; and q is 0, 1, 2, 3, or 4.

compound of the formula (VId-1). In one embodiment, the reducing agent is aluminum triisopropoxide and isopropanol. Preferably, the temperature is maintained above room temperature, more preferably between about 60°C and about 82°C. The product alcohol can be isolated by either cooling the reaction mixture to room temperature, diluting with more isopropanol and collecting the crystalline material or by cooling the reaction to room temperature and adding 1 N HCL and water and collecting the crystalline material.

[0152] Step 2 of scheme 1 includes reacting a compound of the formula R_7-SO_2-X and a compound of the formula (VId-1) in the presence of a base to form the compound of the formula (VIe-1). Any amine base is suitable, including pyridine, triethylamine, N-methylmayholine, and diisoyropylethylamine. In one embodiment, R_7-SO_2-R_8 is p-toluenesulfonic acid, methanesulfonic acid, sulfuric acid, or methanesulfonyl chloride. In another embodiment, the conversion of hydroxy dioxane (VId-1) to dioxane oxazolidinone (VIe-1) can be achieved by treatment of the hydroxy dioxane (Vid-1) with methanesulfonyl chloride and triethylamine in tetrahydrofuran solution and heating the mixture to cause the cyclization of the mesylate formed in situ to the oxazolidinone.

[0153] In step 3 of scheme 1, a compound of the formula (VIf-1) may be formed by heating the compound of the formula (VIe-1). The reaction may proceed by dissolving compound VIe-1 in a solvent such as pyridine or N-methyl imidazole and heating the mixture for several hours at temperature from about 50°C to about 100°C; preferably at about 80°C. The mesylate (VIf-1) may be recovered by extraction into an organic solvent such as ethyl acetate and removal of the amine solvents by extraction of the solution with aqueous acid.

[0154] Step 4 of scheme 1 depicts reacting hydroxylamine hydrochloride, a compound of the formula R_7-SO_2-X, and a compound of the formula (VIf-1) to form a compound of the formula (VIg-1). In one embodiment, R_7-SO2-X is p-toluenesulfonic acid, methanesulfonic acid, sulfuric acid, or methanesulfonyl chloride. The reaction may occur in a solvent, such as methanol. In one embodiment, the reaction occurs in methanol with tosic acid at reflux for 8 to 24 hours. The resulting nitrile oxazolidinone contains a small amount of the corresponding ethyl ester which is not removed since it also is converted to the desired lactone in subsequent steps.

[0155] Step 5 of scheme 1 includes a) hydrolyzing a compound of the formula (VIg-1) with an aqueous solution in the presence of a base, b) protecting the amine group of the compound so formed, and c) cyclizing the compound so formed with heat and an acid catalyst. In one embodiment, the compound VIg-1 is hydrolyzed with sodium hydroxide. The pH is adjusted to approximately 10 and tetrahydrofuran and BOC dicarbonate are added. This provides the protected hydroxy acid, which may be heated in 10% acetic acid and toluene to provide the protected amine lactone (V-1).

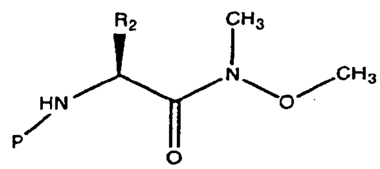
[0156] The compound of formula (V-1) may also be produced according to scheme 2.

pochlorous acid oxidation reaction into a solvent system of tetrahydrofuran and water, followed by addition of a Pd/C catalyst. The resulting mixture is subjected to hydrogen above atmospheric pressure and temperature. In one embodiment, the pressure is about 80 pounds per square inch and the temperature is maintained from about 60°C to about 70°C until the reaction is substantially complete.

[0160] In step 2 of scheme 2, the compound of the formula (VIb-1) may be formed by reacting a silyating agent and a compound of the formula (VIa-1) and reacting the compound so formed with a reducing agent. In one embodiment, the reducing agent is N-selectride. In another emodiment, the silyating agent is 1,1,1,3,3,3-hexamethyl-disilazane. The reduction reaction may occur at temperatures below about 0°C, preferably below about -20°C, more preferably below about - 50°C. In addition, the reducing agent may be present in slight excess.

[0161] In step 3 of scheme 2, the compound of the formula (V-1) is formed by heating a compound of the formula (VIb-1) in the presence of an acid catalyst, such as acetic acid. In one embodiment, the cyclization reaction occurs by introducing the compound VIb-1 into a solvent mixture, such as toluene and 10% acetic acid, at the solvent reflux temperature for 8 to 16 hours. This provides the desired lactone as a crystalline solid after work up.

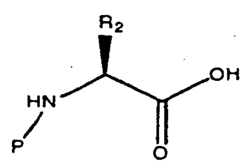
[0162] One method of making the compound of the formula (VI-1) is by reacting a compound of the formula (VII-1)



(VII-1)

with a Grinard reagent formed in situ by addition of 2-(2-bromo-ethyl)-[1,3]dioxane to a mixture comprising magnesium and the compound of the formula (VII-1). In one embodiment, the mixture further comprises methyl magnesium chloride and/or methyl magnesium bromide in a solvent. Any exotherm formed from the reaction may be controlled by the rate of addition of the bromide.

[0163] The compound of the formula (VII-1) may be formed by coupling N,O-dimethylhydroxylamine hydrochloride and a compound of the formula (VIII-1)

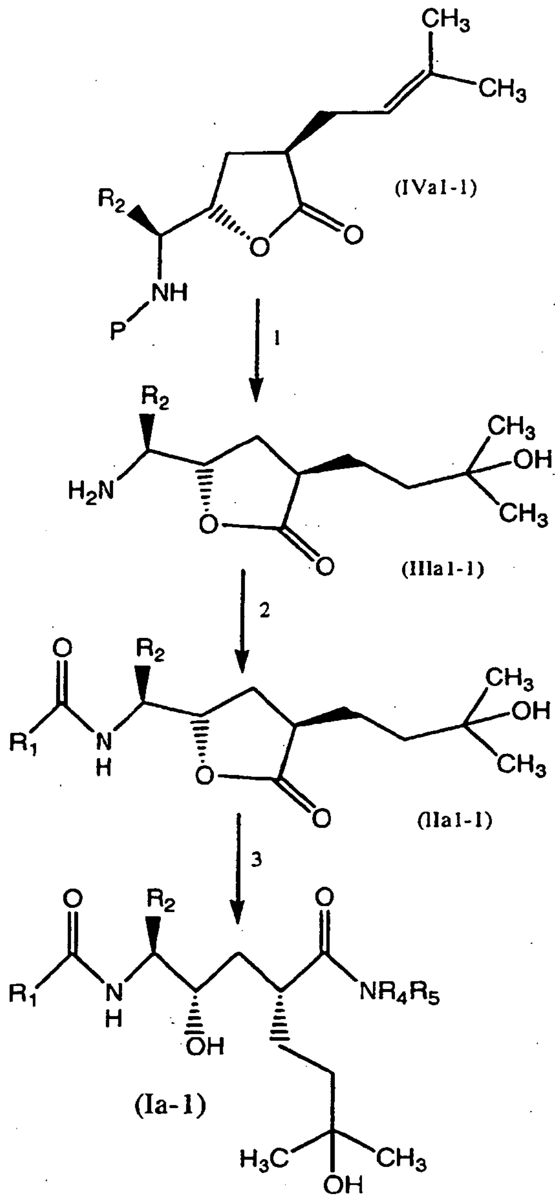


(VIII-1)

This coupling reaction may be performed by mixed anhydride procedure. In one mixed anhydride procedure, compound VIII-1 is combined with methylene chloride and N-methylmorpholine is added followed by isobutyl chloroformate. In a separate mixture, a slurry of N,O-dimethylhydroxylamine hydrochloride is treated with N-methylmorpholine. The two reaction mixtures are combined and then quenched with a solution of citric acid in water. This procedure preferably operates at a temperature below about 20°C, more preferably below about 0°C.

[0164] Compounds of formula (V-1) may be used to produce compounds of the formula (IVa1-1) according to scheme 3:

Scheme 4



(IVa1-1)

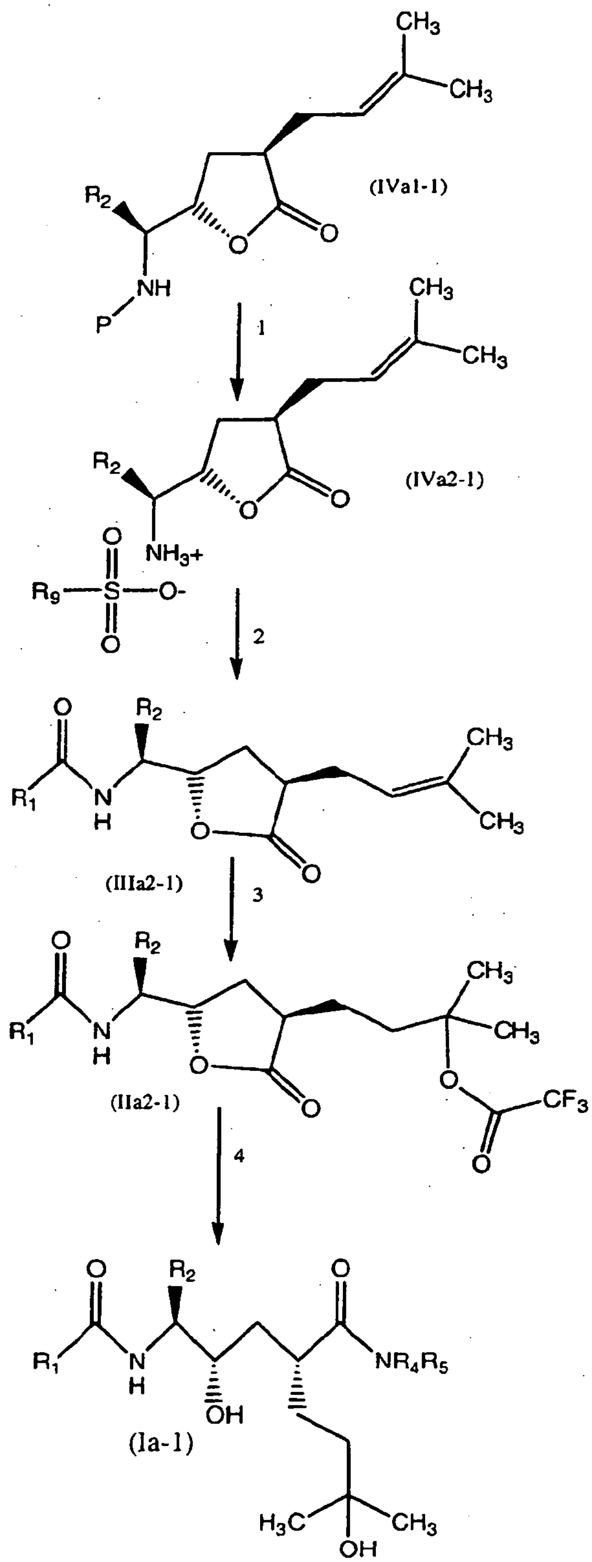
(IIIa1-1)

(IIa1-1)

(Ia-1)

[0167] In step 1 of scheme 4, a compound of the formula (IIIa1-1) is formed by reacting a compound of the formula (IVa1-1) with phosphoric acid. Preferably, this reaction occurs in any suitable solvent, such as non-alcoholic solvents. Two preferred solvents include tetrahydrofuran and dichloroethane. The reaction may take place at any suitable temperature, preferably from about -25ºC to about 120ºC, more preferably from about 15ºC to about 40ºC. Reaction time is dependent on temperature and batch size, amount other factors, but typically reaction time is from about 2 hours to about 14 hours.

[0168] Step 2 of scheme 4 depicts coupling a compound IIIa1-1 with a compound having the formula R_1-CO-X to form a compound having the formula (IIa1-1). This coupling reaction is generally conducted at a temperature from about -30°C to about 80°C, preferably from about 0°C to about 25°C. The coupling reaction may occur with a coupling reagent that activates the acid functionality. Exemplary coupling reagents include dicyclohexylcarbodiimide/hydroxybenzotriazole (DCC/HBT), N-3-dimethylaminopropyl-N'-ethylcarbodiimide (EDC/HBT), 2-ethyoxy-1-ethoxycarbonyl-



Scheme 5

[0171] In step 1 of scheme 5, a compound of the formula (IVa1-1) is reacted with a compound of the formula R_9-SO_2-

DRUG IN NANOPARTICULATE FORM

[0179] The terms "nanoparticulate," and "nanoparticulate form" as employed herein refer to a solubility-improved form of a drug in the form of particles generally having an effective average particle size of less than about 1 um, preferably less than about 400 nm, more preferably less than about 250 nm and even more preferably less than about 100 nm. Examples of such nanoparticulate forms of drug are further described in U.S. Patent No. 5,145,684.

[0180] Such nanoparticulate drug form generally comprises about 10% to 99.9% by weight of a crystalline drug substance having a solubility in water less than about 10 mg/mL and the drug substance having an effective average particle size of less than about 400 nm. As described in U.S. Patent No. 5,145,684, nanoparticulate drug forms preferably consist essentially of 10% to 99.9% by weight of a crystalline drug substance having a solubility in water of less than 10 mg/mL, said drug substance having a non-crosslinked surface modifier adsorbed on the surface thereof in an amount of 0.1 to 90% by weight and sufficient to maintain an effective average particle size of less than about 400 nm.

[0181] Particle size can be measured by conventional particle size measuring techniques well known to those skilled in the art, such as sedimentation field flow fractionation, photon correlation spectroscopy, or disk centrifugation. By "an effective average particle size of less than about 400 nm" is meant that at least 90% of the particles have a weight average particle size of less than about 400 nm when measured by the above-noted techniques. Preferred embodiments of the invention will have an effective average particle size of less than about 250 nm. In some embodiments of the invention, the effective average particle size will be less than about 100 nm. In reference to the effective average particle size, it is contemplated that at least 95% and, and more particularly at least 99% of the particles have a particle size that is less than the effective average, *e.g.*, 400 nm.

[0182] The nanoparticles of the drug can be prepared in a method comprising the steps of dispersing a drug substance in a liquid dispersion medium and applying mechanical means in the presence of grinding media to reduce the particle size of the drug substance to the effective average particle size. The particles can be reduced in size in the presence of a surface modifier. Alternatively, the particles can be contacted with a surface modifier after attrition.

[0183] A general procedure for preparing the nanoparticles is set forth below. The drug substance selected is obtained commercially and/or prepared by techniques known in the art in a conventional coarse form. It is preferred, but not essential, that the particle size of the coarse drug substance selected be less than about 100 μm as determined by sieve analysis. If the coarse particle size of the drug substance is greater than about 100 μm, then it is preferred that the particles of the drug substance be reduced in size to less than 100 μm using a conventional milling method such as airjet or fragmentation milling.

[0184] The coarse drug substance selected can then be added to a liquid medium in which it is essentially insoluble to form a premix. The concentration of the drug substance in the liquid medium can vary from about 0.1-60%, and preferably is from 5-30% (w/w). Although not essential, a surface modifier may be present in the premix.

[0185] The mixture can be used directly by subjecting it to mechanical means to reduce the average particle size in the drug substance to the desired size. It is preferred that the premix be used directly when a ball mill is used for attrition. Alternatively, the drug can be mixed in the liquid medium using suitable agitation, *e.g.*, a roller mill or a Cowles type mixer, until a homogeneous mixture is observed in which there are no large agglomerates visible to the naked eye. It is preferred that the premix be subjected to such a premilling mixing step when a recirculating media mill is used for attrition.

[0186] The mechanical means applied to reduce the particle size of the drug substance conveniently can take the form of a mill. Suitable mills include a ball mill, an attritor mill, a vibratory mill, and media mills such as a sand mill and a bead mill. A media mill is preferred due to the relatively shorter milling time required to provide the intended result, *i.e.*, the desired reduction in particle size. For media milling, the apparent viscosity of the premix preferably is from about 100 to about 1000 centipoise. For ball milling, the apparent viscosity of the premix preferably is from about 1 up to about 100 centipoise. Such ranges tend to afford an optimal balance between efficient particle fragmentation and media erosion.

[0187] The grinding media for the particle size reduction step can be selected from rigid media which are preferably spherical or particulate in form having an average size of less than about 3 mm and, more preferably, less than about 1 mm. Such media desirably can provide the particles of the invention with shorter processing times and impart less wear to the milling equipment. The selection of material for the grinding media is not believed to be critical. Zirconium oxide, such as 95% ZrO stabilized with magnesia, zirconium silicate, and glass grinding media provide particles having levels of contamination which are believed to be acceptable for the preparation of pharmaceutical compositions may be used. However, other media, such as stainless steel, titania, alumina, and 95% ZrO stabilized with yttrium, are expected to be useful. Preferred media have a density greater than about 3 g/cm^3.

[0188] The attrition time can vary widely and depends primarily upon the particular mechanical means and processing conditions selected. For ball mills, processing times of up to five days or longer may be required. On the other hand, processing times of less than 1 day (residence times of one minute up to several hours) may provide the desired results using a high shear media mill.

under continuous rotation, in a vacuum granulator under constant mixing, in a mortar under light mixing with a pestle, or in a fluidized bed with the polymer kept suspended in an air stream. The product obtained is then dried in the aforesaid apparatuses or in other suitable apparatuses.

(1 b) the drug is dissolved in a suitable solvent and a quantity of a water-swellable but water-insoluble crosslinked polymer (or a mixture of two or more such polymers) is suspended in an excess of the solution obtained. The suspension is kept stirred until the polymer particles swell. The suspension is then filtered or separated by other suitable means and the product is recovered and dried.

(1c) the drug in powder form and the water-swellable but water-insoluble crosslinked polymer (or mixture of two or more such polymers) in powder form are homogeneously mixed together and then ground together in a suitable apparatus such as a ball mill, high-energy vibratory mill, air jet mill etc.

(1d) the drug in powder form and the water-swellable but water-insoluble crosslinked polymer in powder form are mixed homogeneously and then heated together to the drug melting point in an apparatus such as an oven, rotary evaporator, reaction vessel, oil bath etc. until the drug has melted and has been absorbed by the polymer.

The weight ratio of the drug to said polymer (or mixture of two or more polymers) is in all cases between 0.1 and 1000 parts by weight of drug per 100 parts by weight of polymer and preferably between 10 and 100 parts by weight of drug per 100 parts by weight of polymer.

2nd stage: In the 2nd stage the polymer in which the drug has been incorporated by any of the methods described for the 1st stage is brought into contact with a solvent in the vapor or liquid state by any suitable method, for example by any of the following:

(2a) the polymer with the drug incorporated is introduced into a chamber into which the solvent in vapor form is fed through a valve. The chamber can be that in which the 1st stage was carried out;

(2b) the polymer with the drug incorporated is introduced into a sealed chamber already saturated with solvent vapor generated by a solvent container situated within the chamber and kept in the sealed chamber until saturation is complete;

(2c) the polymer with the drug incorporated is suspended in a fluidized bed by an air stream and is then sprayed with the liquid solvent or is exposed to an air stream saturated with the solvent vapor;

(2d) the polymer with the drug incorporated is suspended in an excess of solvent in liquid form, for example in a reaction vessel, in a mixer etc., and is then filtered off or separated by other means.

[0196] The time of contact between the polymer with the drug incorporated and the solvent in vapor or liquid form is dependent on the drug/polymer/solvent combination in order to obtain the desired characteristics of high drug concentration in the surface layers and/or transformation of the physical state of the drug into a crystalline state of lower melting point. The treatment with solvent in gaseous form is conducted at a temperature preferably of between 20° and 100°C and the treatment with solvent in liquid form is conducted at a temperature preferably of between 5° and 90°C. The time of contact with the gaseous solvent is between 0.5 and 48 hours when the solvent is not water, and between 12 and 36 hours when the solvent is water. The time of contact with the liquid solvent is between 1 minute and 96 hours when the solvent is water, and between 1 and 15 hours when the solvent is water. The final drying of the product is preferably conducted in an oven under vacuum at a temperature of between 20° and 100°C.

[0197] The solvent (or solvent mixtures) suitable for the method according to the invention are all those which are able to swell the polymer or to be absorbed by the polymer into which the drug has been incorporated. Examples of solvents are water, water-alcohol mixtures, methanol, ethanol, higher alcohols, acetone, chlorinated solvents, formamide, dimethylformamide, fluorinated hydrocarbons and others.

[0198] Examples of water-swellable but water-insoluble crosslinked polymers suitable for use (singly or in combinations of two or more than two) in the process of the invention are: crosslinked polyvinylpyrrolidone (abbreviated to crospovidone) as described in National Formulary XV, Supplement 3, page 368; crosslinked sodium carboxymethylcellulose as described in National Formulary XV, Supplement 3, page 367; crosslinked β-cyclodextrin polymer as described in WO patent 83/00809 and by Fenyvest et al. in Pharmacie, 39, 473, 1984; and crosslinked dextran. Other polymers suitable to form the crosslinked polymer should have a hydrophilic polymer lattice allowing high swellability in water, and a water insolubility as determined by the nature of the polymer lattice.

[0199] Thus, in one embodiment, the absorbed drug form comprises a poorly soluble drug supported on a polymer substance in a form capable of increasing the dissolving rate of the drug, prepared by a method comprising: 1) bringing a drug incorporated into particles of a crosslinked polymer which is swellable in water but insoluble in water by treating the polymer particles with a solution of the drug in a non-aqueous organic solvent and drying, or by mixing the polymer particles with the drug, heating to the drug melting point, and then cooling at ambient temperature; 2) bringing the thus

3. Preferably, the dispersion medium is heated to approximately the temperature of the melt prior to mixing and may contain additives, *e.g.,* stabilizers, isotonicity agents, buffering agents, cryoprotectants and/or preservatives.
4. Optionally, the dispersion medium and the melt are added and predispersed to give a crude dispersion, for example by shaking, stirring, sonication or vortexing. Predispersing is preferably carried out at temperatures above the melting point of the substance or the mixture of substances or the mixture of substances and additives, *e.g.,* stabilizers, respectively. Predispersing can he omitted for well dispersible systems.
5. The melt is then emulsified in the dispersion medium, preferably at temperatures above the melting point of the substance or the mixture of substances or the mixture of substances and additives, *e.g.,* stabilizers, respectively. Emulsification is preferably carried out by high pressure homogenization or by sonication, but may be also possible by high speed stirring, vortexing and vigorous hand shaking.
6. The dispersion can then be further processed into suitable dosage forms.

[0207] A concentration-enhancing polymer may be mixed with the molten drug or the supercooled drug form may first be prepared and then mixed with the concentration-enhancing polymer.

CYCLODEXTRIN/DRUG FORMULATIONS

[0208] Various solubility-improved drug forms using cyclodextrin are well known in the art. As used herein, the term "cyclodextrin" refers to all forms and derivatives of cyclodextrin. Particular examples of cyclodextrin include α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin. Exemplary derivatives of cyclodextrin include mono- or polyalkylated β-cyclodextrin, mono- or polyhydroxyalkylated β-cyclodextrin, hydroxypropyl β-cyclodextrin (hydroxypropylcyclodextrin), mono, tetra or hepta-substituted βcyclodextrin, and sulfoalkyl ether cyclodextrin (SAE-CD). These drug forms, also known as cyclodextrin derivatives, herein after referred to as "cyclodextrin/drug forms" can be simple physical mixtures. An example of such is found in U.S. Patent No. 5,134,127, herein incorporated by reference. For example, the active drug and sulfoalkyl ether cyclodextrin (SAE-CD) may be preformed into a complex prior to the preparation of the final formulation. Alternatively, the drug can be formulated by using a film coating surrounding a solid core comprising a release rate modifier and a SAE-CD/drug mixture, as disclosed in U.S. Patent No. 6,046,177 ('177), herein incorporated by reference. Upon exposure in the use environment, the SAE-CD/drug mixture converts to a complex. Alternatively, controlled-release formulations containing SAE-CD may consist of a core comprising a physical mixture of one or more SAE-CD derivative, an optional release rate modifier, a therapeutic agent, a major portion of which is not complexed to the SAE-CD, and an optional release rate modifying coating surrounding the core. Other cyclodextrin/drug forms contemplated by the invention are found in U.S. Patent Nos. 5,134,127, 5,874,418, and 5,376,645, all of which are incorporated by reference. For example, the drug in cyclodextrin, e.g. SAE-CD, may be physically mixed, wherein a major portion of the drug is not complexed to the SAE-CD in the composition. A preferred SAE-CD is sulfobutyl ether-CD.

DRUG IN THE FORM OF A SOFTGEL

[0209] Another solubility-improved drug form, herein referred to as the "softgel form," generally relates to a drug encapsulated in soft-gelatin. Typically, such softgel forms comprise a soft-gelatin capsule filled with a material, the material often being a highly concentrated solution of drug in a liquid. The fill material generally comprises either a water miscible carrier, such as polyethylene glycol or polyvinylpyrrolidone, or a water immiscible carrier, such as a lipid or oil, in which the drug is dissolved with or without a surfactant or emulsifying agent. The fill material is placed into the soft gelatin capsule, for example, by encapsulating the fill material between two sheets of gelatin as it passes between a pair of die rolls having surface cavities shaped to form the desired shape of the resulting softgel. Such softgel drug forms are well-known and are described in "The Theory and Practice of Industrial Pharmacy", by L. Lachman, H. Lieberman, and J. Kanig, Lea and Febiger, publisher, 3rd Edition, 1986.

[0210] A concentration-enhancing polymer may be blended with the fill material prior to filling the soft gelatin capsule, it may be added separately to the soft-gelatin capsule, or the softgel drug form may first be prepared and then blended with the concentration-enhancing polymer.

[0211] One variation on the softgel form is found in U.S. Patent Nos. 5,071,643 and 5,360,615, the disclosures of which are incorporated herein by reference. These patents disclose a solvent system for enhancing the solubility of a pharmaceutical agent to produce a highly concentrated solution suitable for softgel filling comprising 10 to 80% polyethylene glycol, 1 to 20% by weight of water, and the pharmaceutical agent. The composition also comprises 0.2 to 1.0 mole equivalents of an ionizing agent per mole equivalent pharmaceutical agent. Glycerin or polyvinylpyrrolidone may be added to further enhance the solubility of certain drugs. U.S. Patent No. 5,376,688, herein incorporated by reference, disclose the use of a fill material comprising 0 to 20% water, a solution of a pharmaceutical agent, an ionizing agent, and a solvent selected from the group consisting of diethylene glycol monoethyl ether, polyglycerol oleate, alpha-

cluding an oil or lipid material; a surfactant; and a hydrophilic phase. The materials used are often selected based on the empirical parameter commonly referred to as the hydrophilic-lipophilic balance (HLB value) of the material. Materials with low HLB values are more lipophilic, while those with high HLB values are more hydrophilic. Materials used in self-emulsifying drug form compositions include polyglycolyzed glycerides, polyethoxylated fatty acids, polyethylene glycol fatty acid diesters, polyethylene glycol fatty acid mono- and diester mixtures, polyethylene glycol glycerol fatty acid esters, transesterification products of natural and hydrogenated oils, polyglycerized fatty acids, propylene glycol fatty acid esters, mixtures of propylene glycol esters and glycerol esters, mono- and di-glycerides, tri-glycerides, sterol and sterol derivatives, polyethylene glycol sorbitan fatty acid esters, polyethylene glycol alkyl ethers, sugar esters, polyethylene glycol alkyl phenols, polyoxyethylene-polyoxypropylene block copolymers, sorbitan fatty acid esters, lower alcohol fatty acid esters, ionic surfactants, and mixtures thereof. Examples of self-emulsifying drug forms can be found in U.S. Patent Nos. 6,294,192 B1, 6,054,136, 5,444,041, 5,993,858, 6,054,136, 6,280,770 B1, 6,309,665 B2, 6,312,704 B1, and PCT Patent Application No. WO 01/01960 A1, the disclosures of which are incorporated by reference.

[0221] A concentration-enhancing polymer may be included as part of the self-emulsifying drug form formulation, or the self-emulsifying drug form may first be prepared and then mixed with the concentration-enhancing polymer.

THREE-PHASE FORM

[0222] Another solubility-improved drug form is the "three-phase form." An example of a three-phase form is described in U.S. Patent No. 6,042,847, herein incorporated by reference. Essentially, the three-phase form gives a constant or controlled release of an amorphous active ingredient stabilized with polymers for a single daily peroral application, which is especially suitable for active ingredients existing in amorphous form or in one or more polymorphous forms, which exhibit poor solubility in crystal form depending on the polymorphous form, particle size and the specific surface area of the active ingredient. In general, this form comprises a core consisting of a first and a second phase and a coating representing the third phase. In the first phase the three-phase pharmaceutical form contains an amorphous active ingredient, the water-soluble polymer polyvinylpyrrolidone and a cellulose ether as carriers of the amorphous active ingredient and simultaneously as inhibitors of its crystallization, and a surfactant that improves the solubility of the active ingredient and promotes the absorption of the amorphous active ingredient from gastrointestinal tract. In the second phase it contains a cellulose ether and a mixture of mono-, di- and triglycerides as sustained release agents. The third phase is represented by a poorly soluble or gastro-resistant film coating, which in the first few hours after the application controls the release of the active ingredient and can consist of an ester of hydroxypropylmethylcellulose with phthalic anhydride or of a copolymerizate based on methacrylic acid and ethyl acrylate.

CONCENTRATION-ENHANCING POLYMERS

[0223] Concentration-enhancing polymers suitable for use in the various aspects of the present invention should be pharmaceutically acceptable, and should have at least some solubility in aqueous solution at physiologically relevant pHs (e.g. 1-8). Almost any neutral or ionizable polymer that has an aqueous-solublitity of at least 0.1 mg/mL over at least a portion of the pH range of 1-8 may be suitable.

[0224] It is preferred that the concentration-enhancing polymers be "amphiphilic" in nature, meaning that the polymer has hydrophobic and hydrophilic portions. Amphiphilic polymers are preferred because it is believed that such polymers tend to have relatively strong interactions with the drug and may promote the formation of various types of polymer/drug assemblies in solution. A particularly preferred class of amphiphilic polymers are those that are ionizable, the ionizable portions of such polymers, when ionized, constituting at least a portion of the hydrophilic portions of the polymer. For example, while not wishing to be bound by a particular theory, such polymer/drug assemblies may comprise hydrophobic drug clusters surrounded by the concentration-enhancing polymer with the polymer's hydrophobic regions turned inward towards the drug and the hydrophilic regions of the polymer turned outward toward the aqueous environment. Alternatively, depending on the specific chemical nature of the drug, the ionized functional groups of the polymer may associate, for example, via ion pairing or hydrogen bonds, with ionic or polar groups of the drug. In the case of ionizable polymers, the hydrophilic regions of the polymer would include the ionized functional groups. In addition, the repulsion of the like charges of the ionized groups of such polymers (where the polymer is ionizable) may serve to limit the size of the polymer/drug assemblies to the nanometer or submicron scale. Such drug/concentration-enhancing polymer assemblies in solution may well resemble charged polymeric micellar-like structures. In any case, regardless of the mechanism of action, the inventors have observed that such amphiphilic polymers, particularly ionizable cellulosic polymers such as those listed below, have been shown to interact with drug so as to maintain a higher concentration of drug in an aqueous use environment.

[0225] One class of polymers suitable for use with the present invention comprises neutral non-cellulosic polymers. Exemplary polymers include: vinyl polymers and copolymers having at least one substituent selected from the group comprising hydroxyl, alkylacyloxy, and cyclicamido; vinyl copolymers of at least one hydrophilic, hydroxyl-containing

ically relevant pH and include at least one ionizable substituent, which may be either ether-linked or ester-linked. Exemplary ether-linked ionizable substituents include: carboxylic acids, such as acetic acid, propionic acid, benzoic acid, salicylic acid, alkoxybenzoic acids such as ethoxybenzoic acid or propoxybenzoic acid, the various isomers of alkoxyphthalic acid such as ethoxyphthalic acid and ethoxyisophthalic acid, the various isomers of alkoxynicotinic acid such as ethoxynicotinic acid, and the various isomers of picolinic acid such as ethoxypicolinic acid, etc.; thiocarboxylic acids, such as thioacetic acid; substituted phenoxy groups, such as hydroxyphenoxy, etc.; amines, such as aminoethoxy, diethylaminoethoxy, trimethylaminoethoxy, etc.; phosphates, such as phosphate ethoxy; and sulfonates, such as sulphonate ethoxy. Exemplary ester linked ionizable substituents include: carboxylic acids, such as succinate, citrate, phthalate, terephthalate, isophthalate, trimellitate, and the various isomers of pyridinedicarboxylic acid, etc.; thiocarboxylic acids, such as thiosuccinate; substituted phenoxy groups, such as amino salicylic acid; amines, such as natural or synthetic amino acids, such as alanine or phenylalanine; phosphates, such as acetyl phosphate; and sulfonates, such as acetyl sulfonate. For aromatic-substituted polymers to also have the requisite aqueous solubility, it is also desirable that sufficient hydrophilic groups such as hydroxypropyl or carboxylic acid functional groups be attached to the polymer to render the polymer aqueous soluble at least at pH values where any ionizable groups are ionized. In some cases, the aromatic substituent may itself be ionizable, such as phthalate or trimellitate substituents.

[0235] Exemplary cellulosic polymers that are at least partially ionized at physiologically relevant pHs include: hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose succinate, hydroxypropyl cellulose acetate succinate, hydroxyethyl methyl cellulose succinate, hydroxyethyl cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, hydroxyethyl methyl cellulose acetate succinate, hydroxyethyl methyl cellulose acetate phthalate, carboxyethyl cellulose, ethyl carboxymethyl cellulose (also referred to as carboxymethyl ethyl cellulose), carboxymethyl cellulose, cellulose acetate phthalate, methyl cellulose acetate phthalate, ethyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, hydroxypropyl methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate succinate, hydroxypropyl methyl cellulose acetate succinate phthalate, hydroxypropyl methyl cellulose succinate phthalate, cellulose propionate phthalate, hydroxypropyl cellulose butyrate phthalate, cellulose acetate trimellitate, methyl cellulose acetate trimellitate, ethyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate succinate, cellulose propionate trimellitate, cellulose butyrate trimellitate, cellulose acetate terephthalate, cellulose acetate isophthalate, cellulose acetate pyridinedicarboxylate, salicylic acid cellulose acetate, hydroxypropyl salicylic acid cellulose acetate, ethylbenzoic acid cellulose acetate, hydroxypropyl ethylbenzoic acid cellulose acetate, ethyl phthalic acid cellulose acetate, ethyl nicotinic acid cellulose acetate, and ethyl picolinic acid cellulose acetate.

[0236] The inventors have found the following cellulosic polymers result in exceptional concentration enhancement: hydroxypropyl methyl cellulose acetate succinate (HPMCAS), such as the LF, LG, MF, MG, HF, and HG grades available from Shin-Etsu; cellulose acetate phthalate (CAP), such as the HF and CE grades available from Eastman Chemical; hydroxypropyl methyl cellulose phthalate (HPMCP), such as the NF grade available from Eastman Chemical, cellulose acetate trimellitate (CAT), available from Eastman Chemical; and hydroxypropyl methyl cellulose such as the E3 Prem-LV grade available from Dow.

[0237] Another preferred class of polymers consists of neutralized acidic polymers. By "neutralized acidic polymer" is meant any acidic polymer for which a significant fraction of the "acidic moieties" or "acidic substituents" have been "neutralized"; that is, exist in their deprotonated form. By "acidic polymer" is meant any polymer that possesses a significant number of acidic moieties. In general, a significant number of acidic moieties would be greater than or equal to about 0.1 milliequivalents of acidic moieties per gram of polymer. "Acidic moieties" include any functional groups that are sufficiently acidic that, in contact with or dissolved in water, can at least partially donate a hydrogen cation to water and thus increase the hydrogen-ion concentration. This definition includes any functional group or "substituent," as it is termed when the functional group is covalently attached to a polymer, that has a pK_a of less than about 10. Exemplary classes of functional groups that are included in the above description include carboxylic acids, thiocarboxylic acids, phosphates, phenolic groups, and sulfonates. Such functional groups may make up the primary structure of the polymer such as for polyacrylic acid, but more generally are covalently attached to the backbone of the parent polymer and thus are termed "substituents." Neutralized acidic polymers are described in more detail in commonly assigned provisional patent application U.S. Serial No. 60/300,256 entitled "Pharmaceutical Compositions of Drugs and Neutralized Acidic Polymers" June 22, 2001, the relevant disclosure of which is incorporated by reference.

[0238] While specific concentration-enhancing polymers have been discussed as being suitable for use in the mixtures of the present invention, blends of such concentration-enhancing polymers may also be suitable. Thus, the term "concentration-enhancing polymer" is intended to include blends of concentration-enhancing polymers in addition to a single species of concentration-enhancing polymer.

PREPARATION OF THE COMPOSITIONS

[0239] The compositions of the present invention may be prepared by dry- or wet-mixing the solubility-improved drug

being substantially converted to its lowest solubility form. Typical enhancements of dissolved drug concentration over equilibrium drug concentration may be on the order of 1.25-fold to 20-fold, and in some cases 20-fold to 100-fold. For example, where the control provides an equilibrium concentration of 1 mg/mL and the composition provides a maximum drug concentration of 1.25 mg/mL, the composition provides a 1.25-fold enhancement.

[0247] It is believed the concentration-enhancing polymers act to slow the rate of precipitation or crystallization of the drug after the drug is initially dissolved. As mentioned previously, because conversion of dissolved drug to a lower solubility form than that of the original solubility-improved form can occur rapidly relative to dissolution, the presence of the polymer may allow a much higher total dissolved drug concentration than is possible in its absence. The presence of the concentration-enhancing polymer(s) thus allows the initially increased or enhanced concentration provided by the drug form to be at least partially maintained for at least a few minutes and, in some cases, for many hours.

[0248] The concentration-enhancing polymers of the present invention provide enhanced concentration of the drug in a use environment exceeding the equilibrium concentration for a longer period of time than a control composition comprising an equivalent quantity of the drug form when subjected to a dissolution test. That is, even though the control composition may provide an enhanced concentration of drug in the use environment that exceeds the equilibrium concentration, the control does so for a shorter period of time than the compositions of the present invention which contain a concentration-enhancing polymer. Preferably, a composition of the present invention provides an enhanced drug concentration that exceeds the equilibrium concentration for a period of at least 15 minutes, preferably a period of at least 30 minutes, preferably a period of at least 60 minutes, and even more preferably a period of at least 90 minutes longer than does the drug concentration provided by a control composition that does not contain the concentration-enhancing polymer.

[0249] As used herein, the term "concentration of drug" in solution or in a use environment refers to drug that may be dissolved in the form of solvated monomeric molecules, so called "free drug," or any other drug-containing submicron structure, assembly, aggregate, colloid, or micelle. As used herein, a "use environment" can be either the *in vivo* environment of the GI tract, subdermal, intranasal, buccal, intrathecal, ocular, intraaural, subcutaneous spaces, vaginal tract, arterial and venous blood vessels, pulmonary tract or intramuscular tissue of an animal, such as a mammal and particularly a human, or the *in vitro* environment of a test solution, such as phosphate buffered saline (PBS) or a Model Fasted Duodenal (MFD) solution. An appropriate PBS solution is an aqueous solution comprising 20 mM sodium phosphate, 47 mM potassium phosphate, 87 mM NaCl and 0.2 mM KCl, adjusted to pH 6.5. An appropriate MFD solution is the same PBS solution wherein additionally is present 7.3 mM sodium taurocholic acid and 1.4 mM of 1-palmitoyl-2-oleyl-sn-glycero-3-phosphocholine.

[0250] A composition of the invention can be tested *in vivo* or, more conveniently, *in vitro* to ascertain whether it is within the scope of the invention. A composition can be dissolution-tested by adding it to a PBS or an MFD solution and agitating to promote dissolution. For example, a composition or a method for administration of drug that meets at least one or more of the concentration criteria in either PBS or MFD or meets one or more of the concentration or bioavailability criteria when dosed orally to the GI tract of an animal, including a mammal such as a human, is a composition or method of this invention.

[0251] In one aspect, the compositions of the present invention comprising a drug in a solubility-improved form combined with a concentration-enhancing polymer provide a maximum concentration of the drug in a use environment that is at least 1.25-fold the maximum concentration of drug in the use environment provided by a control composition comprising an equivalent amount of the drug form but without concentration-enhancing polymer present. The conventional or control composition is the drug form alone or combined with a weight of inert diluent equivalent to the weight of concentration-enhancing polymer in the inventive composition. Preferably, the maximum concentration of drug achieved with the composition of the present invention is at least 2-fold and more preferably at least 3-fold the maximum concentration provided by the control.

[0252] In making such comparisons using this dissolution test or any of the dissolution tests or bioavailability tests described below, it is important that the total amount of drug form dosed be sufficiently high that meaningful comparisons can be made. Specifically, both the compositions of this invention and the control compositions must be dosed at a level at least 2-fold and preferably at 4-fold, and more preferably at least 10-fold, the maximum drug concentration achieved by the control composition.

[0253] Alternatively, the compositions of the present invention provide a dissolution AUC for any period of at least 90 minutes between the time of introduction into the use environment and about 270 minutes following introduction to the use environment that is at least 1.25-fold that of a dissolution AUC provided by a control composition comprising an equivalent quantity of drug form but not containing the concentration-enhancing polymer. Dissolution AUC is the integration of a plot of the drug concentration versus time over a specified time period. For purposes of determining whether a composition or method is part of this invention, the dissolution AUC is calculated over a time period of at least 90 minutes. The time period may be chosen for any time period between the time of introduction into the use environment (time=0) and about 270 minutes following introduction into the use environment. Thus, among the many acceptable time periods are included, for example, (1) from the time of introduction into the use environment to 90

there is provided in the use environment a maximum concentration of the drug that is at least 1.25-fold that of the maximum concentration provided by the drug form in the use environment of the patient without the polymer present.

[0262] In another aspect of the invention, a method is provided for co-administering (1) the drug form and (2) a concentration-enhancing polymer. The concentration-enhancing polymer is co-administered in a sufficient amount so that there is provided in the use environment a dissolution area under the concentration-versus-time curve (AUC) for any period of at least 90 minutes between the time of introduction into the use environment and about 270 minutes following introduction to the use environment that is at least 1.25-fold the corresponding area under the curve provided by the same control composition mentioned above.

[0263] In another aspect of the invention, a method is provided for co-administering (1) the drug form, and (2) a concentration-enhancing polymer. The concentration-enhancing polymer is co-administered in a sufficient amount so that there is provided a relative bioavailability that is at least 1.25-fold relative to the same control composition mentioned above.

EXCIPIENTS AND DOSAGE FORMS

[0264] Although the key ingredients present in the compositions of the present invention are simply the drug form and the concentration-enhancing polymer(s), the inclusion of other excipients in the composition may be useful. These excipients may be utilized with the drug form/concentration-enhancing polymer mixture in order to formulate the mixture into tablets, capsules, suspensions, powders for suspension, creams, transdermal patches, depots, and the like. Drug and concentration-enhancing polymer can be added to other dosage form ingredients in essentially any manner that does not substantially alter the drug form. In addition, as described above, the drug form and the concentration-enhancing polymer may be mixed with excipients separately to form different beads, or layers, or coatings, or cores or even separate dosage forms.

[0265] One very useful class of excipients is surfactants. Suitable surfactants include fatty acid and alkyl sulfonates; commercial surfactants such as benzethanium chloride (HYAMINE® 1622, available from Lonza, Inc., Fairlawn, N.J.); DOCUSATE SODIUM (available from Mallinckrodt Spec. Chem., St. Louis, MO); polyoxyethylene sorbitan fatty acid esters (TWEEN®, available from ICI Americas Inc., Wilmington, DE); LIPOSORB® P-20 (available from Lipochem Inc., Patterson NJ); CAPMUL® POE-0 (available from Abitec Corp., Janesville, WI), and natural surfactants such as sodium taurocholic acid, 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine, lecithin, and other phospholipids and mono- and diglycerides. Such materials can advantageously be employed to increase the rate of dissolution by facilitating wetting, thereby increasing the maximum dissolved concentration, and also to inhibit crystallization or precipitation of drug by interacting with the dissolved drug by mechanisms such as complexation, formation of inclusion complexes, or formation of micelles. These surfactants may comprise up to 5 wt% of the composition.

[0266] The addition of pH modifiers such as acids, bases, or buffers may also be beneficial, retarding the dissolution of the composition (*e.g.*, acids such as citric acid or succinic acid when the polymer is anionic) or, alternatively, enhancing the rate of dissolution of the composition (*e.g.*, bases such as sodium acetate or amines when the polymer is anionic).

[0267] Conventional matrix materials, complexing agents, solubilizers, fillers, disintegrating agents (disintegrants), or binders may also be added as part of the composition itself or added by granulation via wet or mechanical or other means. These materials may comprise up to 90 wt% of the composition.

[0268] Examples of matrix materials, fillers, or diluents include lactose, mannitol, xylitol, dextrose, sucrose, sorbitol, compressible sugar, microcrystalline cellulose, powdered cellulose, starch, pregelatinized starch, dextrates, dextran, dextrin, maltodextrin, calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, magnesium carbonate, magnesium oxide, poloxamers such as polyethylene polypropylene oxide, and hydroxypropyl methyl cellulose.

[0269] Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, methyl cellulose, microcrystalline cellulose, powdered cellulose, starch, pregelatinized starch, and sodium alginate.

[0270] Examples of tablet binders include acacia, alginic acid, carbomer, carboxymethyl cellulose sodium, dextrin, ethylcellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, liquid glucose, maltodextrin, polymethacrylates, povidone, pregelatinized starch, sodium alginate, starch, sucrose, tragacanth, and zein.

[0271] Examples of lubricants include calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc, and zinc stearate.

[0272] Examples of glidants include silicon dioxide, talc, and cornstarch.

[0273] Other conventional form excipients may be employed in the compositions of this invention, including those excipients well-known in the art. Generally, excipients such as pigments, lubricants, flavorants, and so forth may be

Willy A. Bachoffen AG Maschinenfabrik) with silica glass spheres. Milling will continue until the average particle size is less than about 400 nm. Particle size can be measured by using a DuPont sedimentation field flow factionator. A concentration-enhancing polymer is added to the milled mixture in an amount effective to achieve concentration enhancement. A suitable concentration-enhancing polymer is the MF grade of hydroxypropyl methyl cellulose acetate succinate (HPMCAS-MF, available from Shin Etsu). The concentration of drug in solution of the milled pharmaceutical composition can be measured as outlined *supra.* This can be compared to a control composition manufactured identically as above without the concentration-enhancing polymer.

EXAMPLE 2

[0285] A 600 ml cylindrical glass vessel is filled approximately halfway with zirconium oxide grinding spheres with diameters in the range of about 0.85-1.18 mm (Zircoa, Inc.). Then, about 10.8 g of micronized Danazol, about 3.24 g of PVP and about 201.96 g water are added to the glass vessel. The glass vessel is rotated horizontally about its axis at 57% of the "critical speed." The critical speed is defined as the rotational speed of the grinding vessel when centrifuging of the grinding media occurs. At this speed the centrifugal force acting on the grinding spheres presses and holds them firmly against the inner wall of the vessel. Conditions that lead to unwanted centrifuging can be computed from simple physical principles.

[0286] After about 5 days of ball milling, the slurry is separated from the grinding media through a screen and evaluated for particle size with the sedimentation field flow fractionator. The number average particle diameter should be less than about 400 nm, preferably less than about 100 nm. A concentration-enhancing polymer is then added in an amount effective to achieve concentration enhancement. Suitable concentration-enhancing polymers include HPMCAS, CAT, CAP, HPMCP and HPMC. Testing is then conducted as in Example 1 using a control that does not have the concentration-enhancing polymer.

EXAMPLE 3

[0287] A cylindrical glass vessel having a diameter of 2.75 inches (7.0 cm) with a volume of 400 ml is charged with 212 ml of unleaded glass grinding media. Then, about 30.4 g of micronized Danazol, about 9.12 g of PVP, and about 112.48 g of high purity water is added to the vessel. The vessel is rotated horizontally on its axis at a controlled rotational speed of about 80.4 revolutions per minute (50% of critical speed) for about 5 days. The slurry is immediately separated from the grinding media and evaluated for particle size and grinding media attrition using inductively coupled plasma emissions (ICP). The particle size measured with a sedimentation field flow fractionator should yield a number average diameter of less than 400 nm, but preferably between about 110 nm and 180 nm. A concentration-enhancing polymer is then added in an amount effective to achieve concentration enhancement. Suitable concentration-enhancing polymers include HPMCAS, CAT, CAP, HPMCP and HPMC. Testing is then conducted as in Example 1 using a control that does not have the concentration-enhancing polymer.

EXAMPLE 4

[0288] To a 3 gallon porcelain jar, about 6100 ml of unleaded glass spheres with diameter of between 0.85-1.18 mm are added. Then, about 1000 g of micronized Danazol, about 300 g of PVP, and about 3700 g high purity water are added. The vessel is rolled about 5 days at a rotational speed of 39.5 revolutions per minute (50% critical speed). The liquid slurry is separated from the grinding media with a screen and used to prepare solid oral doses. Average particle size should be less than 400 nm, but more preferably, it should be between 135- 225 nm. A concentration-enhancing polymer is then added in an amount effective to achieve concentration enhancement. Suitable concentration-enhancing polymers include HPMCAS, CAT, CAP, HPMCP and HPMC. Testing is then conducted as in Example 1 using a control that does not have the concentration-enhancing polymer.

EXAMPLE 5

[0289] A media mill equipped with a 50 ml grinding chamber ("Mini" Motormill manufactured by Eiger Machinery Inc.) can be used to manufacture nanoparticulate form of a drug. About 27 g of PVP can be dissolved in about 183 g of water and agitated in a steel vessel with a 50 mm "Cowles" type blade until the solution is clear and free of undissolved PVP polymer. The rotational speed of the mixer should be maintained at 5000 RPM. About 90 g of micronized Danazol is slowly added to this blend with the same mixing for 30 min. Then, about 200 cc of this mix is added to a holding tank of a media mill and recirculated. The mill should contain about 42.5 ml of unleaded glass beads (Glens Mills) having diameters ranging between 0.75 mm and 1.0 mm. The final average particle size should be less than about 400 nm, preferably between about 80 nm and 165 nm. A concentration-enhancing polymer is then added in an amount effective

EXAMPLE 13

[0297] Example 12 can be repeated except that Pluronic F68 is replaced with Centrolex® P (a lecithin derivative).

EXAMPLE 14

[0298] 1st stage: 10 g of crospovidone (Kollidon C1, BASF) is swollen by slow addition of 20 ml of a 100 mg/ml solution of griseofulvin in dimethylformamide, mixing the powder continuously in a mortar. The powder swollen in this manner is then placed in an oven under vacuum at a temperature of 100°C for about 12 hours or until completely dried.
[0299] 2nd stage: 2 g of the product obtained in the first stage is disintegrated through a sieve (14 mesh) and then placed in a hermetically sealed container at ambient temperature, saturated with methylenechloride vapor from a receptacle filled with this solvent and placed in the container. After about 24 hours the powder treated in this manner is dried for about 1 hour at 30°C in an oven under vacuum, sieved through a 14 mesh sieve and mixed for 10 minutes.
[0300] A concentration-enhancing polymer is then added in an amount effective to achieve concentration enhancement. A suitable concentration-enhancing polymer is the MF grade of hydroxypropyl methyl cellulose acetate succinate (HPMCAS-MF, available from Shin Etsu). The concentration of drug in a use environment from the resultant pharmaceutical composition can be measured as outlined *supra.* This can be compared to a control composition manufactured identically as above without the concentration-enhancing polymer.

EXAMPLE 15

[0301] 1st stage: 10 g of crospovidone (Knollidon C1, BASF) is swollen by slow addition of 2 ml of a 100 mg/ml solution of griseofulvin in dimethylformamide, mixing the powder continuously in a mortar. The powder swollen in this manner is then placed in an oven under vacuum at a temperature of 100°C for about 12 hours or until completely dried.
[0302] 2nd stage: 2 g of the powder obtained in the first stage is placed in a drier at ambient temperature and under an internal humidity of 90-92% obtained by an aqueous solution of suitable salts placed at the base of the same drier below the perforated floor on which the powder to be treated is placed. After about 24 hours the powder treated in this manner is dried for about 1 hour at 80°C in an oven under vacuum, sieved through a 14 mesh sieve and mixed for 10 minutes.
[0303] A concentration-enhancing polymer is then added in an amount effective to achieve concentration enhancement. Suitable concentration-enhancing polymers include hydroxypropyl methyl cellulose acetate succinate (HPMCAS), cellulose acetate trimellitate (CAT), cellulose acetate phthalate (CAP), hydroxypropyl methyl cellulose phthalate (HPMCP), and hydroxypropyl methyl cellulose (HPMC). The concentration of drug in a use environment from the resultant pharmaceutical composition can be measured as outlined *supra.* This can be compared to a control composition manufactured identically as above without the concentration-enhancing polymer.

EXAMPLE 16

[0304] 1st stage: 10 g of crospovidone (Kollidon C1, BASF) is swollen by slow addition of 20 ml of a 100 mg/ml solution of griseofulvin in dimethylformamide, mixing the powder continuously in a mortar. The powder swollen in this manner is then placed in an oven under vacuum at a temperature of 100°C for about 12 hours or until completely dried.
[0305] 2nd stage: 1 g of the powder obtained in the first stage is wetted with 1 ml of demineralized water in a mortar, mixing the powder slowly for about 1.5 hours. The swollen powder is dried for about 1 hour at 80°C in an oven under vacuum. It is then disintegrated through a 14 mesh sieve and mixed for 10 minutes.
[0306] A concentration-enhancing polymer is then added in an amount effective to achieve concentration enhancement. Suitable concentration-enhancing polymers include HPMCAS, CAT, CAP, HPMCP and HPMC. The concentration of drug in a use environment from the resultant pharmaceutical composition can be measured as outlined *supra.* This can be compared to a control composition manufactured identically as above without the concentration-enhancing polymer.

EXAMPLE 17

[0307] 1st stage: 500 g of crospovidone is swollen with 1000 ml of a 100 mg/ml solution of griseofulvin in dimethylformamide, this solution being added to the crospovidone kept mixing in a high-speed granulator. The swollen powder is then dried in an oven under vacuum at 100°C for about 12 hours and then disintegrated through a 14 mesh sieve and mixed for 10 minutes.
[0308] 2nd stage: 100 g of the powder obtained in the first stage is suspended in a air-operated fluidized bed (GLATT) provided with a spraying apparatus (WURSTER) and sprayed with 200 ml of demineralized water in one hour. They

immersed in a water bath heated to 70°C then allowed to stand at room temperature for cooling.

[0318] A concentration-enhancing polymer is then added in an amount effective to achieve concentration enhancement. Suitable concentration-enhancing polymers include HPMCAS, CAT, CAP, HPMCP and HPMC. The concentration of drug in a use environment from the resultant pharmaceutical composition can be measured as outlined *supra*. This can be compared to a control composition manufactured identically as above without the concentration-enhancing polymer.

EXAMPLE 22

[0319] 2.5 g ubidecarenone is melted in a thermostatized vessel at 70°C. 450 mg lecithin (Phospholipon 100, Nattermann) is added to the melt by sonication (Soniprep. MSE). 210 mg sodium glycocholate is dissolved in 46.8 g bidistilled water, and the solution is heated to 70°C. The heated aqueous phase is added to the mix of lecithin in molten ubidecarenone. Probe sonication (Soniprep. MSE) for 120 min at 70°C yields a fine mixture of ubidecarenone nanoparticles. After cooling to room temperature evaporated water is substituted. The mixture is centrifuged at 4000 rpm in a laboratory centrifuge for 20 min to remove metal shed of the sonication probe.

[0320] A concentration-enhancing polymer is then added in an amount effective to achieve concentration enhancement. Suitable concentration-enhancing polymers include HPMCAS, CAT, CAP, HPMCP and HPMC. The concentration of drug in a use environment from the resultant pharmaceutical composition can be measured as outlined *supra*. This can be compared to a control composition manufactured identically as above without the concentration-enhancing polymer.

Examples 23-29

[0321] For Examples 23-29, a complex of ziprasidone mesylate and sulfobutyl ether cyclodextrin (SBECD) was formed, and the complex was mixed with various concentration-enhancing polymers. The dissolution performance of each complex/polymer mixture was evaluated in *in vitro* tests.

[0322] The ziprasidone complex was formed using the following procedure. First, 1.1374 g SBECD was dissolved in 3.16 g water, by stirring in a 37°C temperature-controlled chamber for about 5 minutes. Next, 0.2169 g of ziprasidone mesylate was added, and the solution was removed from the warm chamber and stirred at ambient temperature for about 1 minute. The clear solution was frozen, and the water was removed by lyophilization to obtain a dry powder. The complex contained 16.02 wt% ziprasidone mesylate, or 11.74 wt% active drug.

[0323] The dissolution of ziprasidone from the complex mixed with various concentration-enhancing polymers was evaluated in an *in vitro* dissolution test using a microcentrifuge method. A 6.13 mg sample of the ziprasidone complex was placed into a microcentrifuge tube with 0.061 mg (1 wt%), 0.307 mg (5 wt%), or 0.613 mg (10 wt%) of polymer. The polymer amounts are expressed as wt% based on the weight of the complex. Example 23 comprised a mixture of the complex with 1 wt% HPMCAS, MF grade (HPMCAS-MF, from Shin Etsu, Tokyo, Japan). Example 24 comprised a mixture of the complex with 5 wt% HPMCAS-MF. Example 25 comprised a mixture of the complex with 10 wt% HPMCAS-MF. Example 26 comprised a mixture of the complex with 1 wt% HPMCAS, HF grade (HPMCAS-HF, from Shin Etsu, Tokyo, Japan). Example 27 comprised a mixture of the complex with 1 wt% CAP (NF grade from Eastman Chemical Co., Kingsport, Tennessee). Example 28 comprised a mixture of the complex with 1 wt% carboxymethylethyl cellulose (CMEC) (Freund Industrial Co. Ltd., Tokyo, Japan). Example 29 comprised a mixture of the complex with 5 wt% CMEC. Tests were performed in duplicate. The tubes were placed in a 37°C temperature-controlled chamber, and 1.8 mL of 50 mM 4-morpholinepropanesulfonic acid (MOPS) buffer with 150 mM NaCl (pH 7.4) was added. The samples were quickly mixed using a vortex mixer for about 60 seconds. The samples were centrifuged at 13,000 G at 37°C for 1 minute. The resulting supernatant solution was then sampled and diluted 1:4 (by volume) with methanol and then analyzed by high-performance liquid chromatography (HPLC). A Phenomenex Ultracarb 5 ODS HPLC column was used with a mobile phase of 60 vol.% of 0.02 M KH_2PO_4(pH 3.0), and 40 vol.% acetonitrile. UV detection was measured at 254 nm. The contents of the tubes were mixed on the vortex mixer and allowed to stand undisturbed at 37°C until the next sample was taken. Samples were collected at 4, 10, 30, 60, and 90 minutes. For Control 1 (C1), 6.13 mg of ziprasidone complex was tested without concentration-enhancing polymer in the test solution. °Control 2 (C2) consisted of 0.982 mg ziprasidone mesylate alone. The concentrations of drug obtained in these samples are shown below.

Table 1 (continued)

Example	Time (min)	Ziprasidone Concentration (μg/mL)	AUC (min*μg/mL)
29 SBECD complex + 5 wt% CMEC	0	0	0
	4	276	600
	10	174	1900
	30	46	4100
	60	41	5400
	90	46	6700
C1 SBECD complex	0	0	0
	4	12	0
	10	10	100
	30	7	300
	60	6	500
	90	8	700
C2 Ziprasidone Mesylate	0	0	0
	4	3	0
	10	1	0
	30	1	0
	60	1	0
	90	1	100

Results from dissolution tests of Examples 23-29, and Controls C1 and C2, are summarized in Table 2.

Table 2

Example	Concentration Enhancing Polymer*	Amount of Polymer (wt% of complex)	$C_{max,90}$ (μg/mL)	AUC_{90} (min*μg/mL)
23	HPMCAS-MF	1	204	6800
24	HPMCAS-MF	5	227	6300
25	HPMCAS-MF	10	254	6800
26	HPMCAS-HF	1	194	3600
27	CAP	1	196	6900
28	CMEC	1	236	5600
29	CMEC	5	276	6700
C1 SBECD complex	none	--	12	700
C2 ziprasidone mesylate	none	--	3	100

*Polymer designations: HPMCAS = hydroxypropylmethyl cellulose acetate succinate, CAP = cellulose acetate phthalate, CMEC = carboxymethylethyl cellulose.

[0324] As can be seen from the data in Table 2, the ziprasidone complex mixed with concentration-enhancing polymers provides C_{max90} values 16- to 23-fold that of the complex alone, and AUC_{90} values 5- to 10-fold that of the complex alone. The dissolution performance of the complex (C1) compared to drug alone (C2) shows that the complex is a

Table 3 (continued)

Example	Time (mins)	Ziprasidone Concentration (μg/mL)	AUC (min*μg/mL)
C3 SBECD complex	0	0	0
	4	9	0
	10	11	100
	30	5	200
	60	10	500
	90	6	700
C4 HPCD complex	0	0	0
	4	10	0
	10	6	100
	30	6	100
	60	16	300
	90	15	1100

Results from dissolution tests of Examples 30-33, and Controls C3 and C4, are summarized in Table 4.

Table 4

Example	Cyclodextrin	$C_{max,90}$ (μg/mL)	AUC_{90} (min*μg/mL)
30	SBECD	167	3700
31	HPCD	52	2600
32	β-CD	36	2600
33	γ-CD	18	1000
C3 no polymer	SBECD	11	700
C4 no polymer	HPCD	16	1100

[0328] As can be seen from the data in Table 4, the ziprasidone SBECD complex mixed with concentration-enhancing polymer provides a C_{max90} 15.2-fold that of Control C3, and an AUC_{90} 5.3-fold that of Control C3. The ziprasidone HPCD complex mixed with concentration-enhancing polymer provides a C_{max90} 3.3-fold that of Control C4, and an AUC_{90} 2.4-fold that of Control C4. Examples 32 and 33 provided C_{max90} values 12- and 6-fold that of the drug alone (C2, Table 2), and AUC_{90} values 26- and 10-fold that of the drug alone.

[0329] The invention has been described in detail with particular reference to particular embodiments thereof, but it will be understood that variations and modifications can be effected within the spirit and scope of the invention.

Claims

1. A composition comprising

(a) a drug in a solubility-improved form which provides, when administered to a use environment, at least one of a dissolved drug concentration in said use environment that exceeds an equilibrium concentration of a lowest solubility form of said drug in said use environment and a dissolution rate that exceeds a dissolution rate of said lowest solubility form of said drug in said use environment; and

(b) a concentration-enhancing polymer wherein said concentration-enhancing polymer is present in a sufficient amount so that said composition provides, after introduction into said use environment, a maximum concen-

lulose, ethyl carboxymethyl cellulose, carboxymethyl cellulose, carboxymethyl ethyl cellulose, cellulose acetate phthalate, methyl cellulose acetate phthalate, ethyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, hydroxypropyl methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate succinate, hydroxypropyl methyl cellulose acetate succinate phthalate, hydroxypropyl methyl cellulose succinate phthalate, cellulose propionate phthalate, hydroxypropyl cellulose butyrate phthalate, cellulose acetate trimellitate, methyl cellulose acetate trimellitate, ethyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate succinate, cellulose propionate trimellitate, cellulose butyrate trimellitate, cellulose acetate terephthalate, cellulose acetate isophthalate, cellulose acetate pyridinedicarboxylate, salicylic acid cellulose acetate, hydroxypropyl salicylic acid cellulose acetate, ethylbenzoic acid cellulose acetate, hydroxypropyl ethylbenzoic acid cellulose acetate, ethyl phthalic acid cellulose acetate, ethyl nicotinic acid cellulose acetate, or ethyl picolinic acid cellulose acetate, or a neutralised form of any thereof.

7. A composition according to any of Claims 1 to 3 wherein said polymer is hydroxypropyl methyl cellulose acetate, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl cellulose, hydroxyethyl methyl cellulose, hydroxyethyl cellulose acetate, or hydroxyethyl ethyl cellulose.

8. A composition according to any of Claims 1 to 3 wherein said polymer is a carboxylic acid-functionalised polymethacrylate, a carboxylic acid-functionalised polyacrylate, an amine-functionalised polyacrylate, an amine-fuctionalised polyacrylate or polymethacrylate, a protein, or a carboxylic acid-functionalised starch.

9. A composition according to any of Claims 1 to 3 wherein said polymer is a vinyl polymer or copolymer having at least one substituent selected from the group comprising hydroxyl, alkylacyloxy, and cyclicamido, a vinyl copolymer having at least one hydrophilic, hydroxyl-containing repeat unit and at least one hydrophobic, alky- or aryl-containing repeat unit, a polyvinyl alcohol having at least a portion of its repeat units in the unhydrolysed (vinyl acetate) form, a polyvinyl alcohol-polyvinyl acetate copolymer, a polyvinylpyrrolidone, a polyethylene-polyvinyl alcohol copolymer, or a polyoxyethylene-polyoxypropylene block copolymer.

10. A composition according to any of Claims 1 to 3 wherein said polymer is hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, carboxymethyl ethyl cellulose, polyvinyl alcohols, polyvinylpyrrolidone, polyoxyethylene-polyoxypropylene block copolymers, or a blend of any thereof.

11. A composition according to any of Claims 1 to 3 wherein said solubility-improved drug form is the cyclodextrin/drug form, said drug is ziprasidone, and said polymer is hydroxypropyl methyl cellulose acetate succinate, cellulose acetate phthalate, or carboxymethyl ethyl cellulose.

12. A composition according to any of Claims 1 to 3 wherein the solubility-improved drug form comprises a CETP inhibitor or a CCR1 inhibitor.

13. A composition according to any of Claims 1 to 12 for use as a medicament.

14. The use of a drug in a solubility-improved form which provides, when administered to a use environment, at least one of a dissolved drug concentration in said use environment that exceeds an equilibrium concentration of a lowest solubility form of said drug in said use environment and a dissolution rate that exceeds a dissolution rate of said lowest solubility form of said drug in said use environment, for the manufacture of a medicament combined with a concentration-enhancing polymer for the treatment of a condition for which is required a maximum concentration of said drug in said use environment that is at least 1.25-fold a maximum concentration of said drug provided by a control composition, wherein said control composition is an equivalent quantity of said drug in said solubility-improved form alone.

15. The use of a drug in a solubility-improved form which provides, when administered to a use environment, at least one of a dissolved drug concentration in said use environment that exceeds an equilibrium concentration of a lowest solubility form of said drug in said use environment and a dissolution rate that exceeds a dissolution rate of said lowest solubility form of said drug in said use environment, for the manufacture of a medicament combined with a concentration-enhancing polymer for the treatment of a condition for which is required a dissolution area under the concentration versus time curve for any period of at least 90 minutes between the time of introduction into the use environment and about 270 minutes following introduction into the use environment that is at least

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 269 994 A3

(12) EUROPEAN PATENT APPLICATION

(88) Date of publication A3:
12.02.2003 Bulletin 2003/07

(51) Int Cl.7: A61K 9/14

(43) Date of publication A2:
02.01.2003 Bulletin 2003/01

(21) Application number: 02253951.4

(22) Date of filing: 06.06.2002

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: 22.06.2001 US 300314 P

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(54) Pharmaceutical compositions comprising drug and concentration-enhancing polymers

(57) A solubility-improved drug form is combined with a concentration-enhancing polymer in a sufficient amount so that the combination provides substantially enhanced drug concentration in a use environment relative to a control comprising the same amount of the same drug form without the concentration-enhancing polymer.

EP 1 269 994 A3

Printed by Jouve, 75001 PARIS (FR)

European Patent Office

INCOMPLETE SEARCH SHEET C

Application Number
EP 02 25 3951

Although claims 14-19 are directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

Claim(s) searched completely:
1-13

Claim(s) searched incompletely:
14-19

Reason for the limitation of the search (non-patentable invention(s)):

Article 52 (4) EPC - Method for treatment of the human or animal body by therapy

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 02 25 3951

Category	DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
P,X	WO 01 47495 A (CURATOLO WILLIAM JOHN ;FRIESEN DWAYNE THOMAS (US); LORENZ DOUGLAS) 5 July 2001 (2001-07-05) * page 7, line 12 - page 9, line 3 * * page 10, line 23 - page 11, line 18 * * page 51, line 8 - page 72, line 30; examples * * claims 1,4,5,8-24 * ---	1-7,9, 10,12-19	
P,X	US 2002/006443 A1 (NIGHTINGALE JAMES A S ET AL) 17 January 2002 (2002-01-17) * page 1, paragraph 1 - paragraph 2 * * page 12, paragraph 94 - page 13, paragraph 98 * * examples * * claims 1,12-14,20,24-30,146,155 * * page 2, paragraph 17 - page 3, paragraph 23 * ---	1-7,9, 10,12-19	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
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